



# A registry-based study of cancer and reproduction

—fertility after cancer, outcomes in the offspring, and survival of pregnancy-associated cancer

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PhD thesis



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National Resource Centre for Late Effects after Cancer Treatment*



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*To the men in my life*

*–Johan, Steinar, Geir, Gabriel, and Amandus*



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## Abbreviations

|        |   |
|--------|---|
| ABVD   | Chemotherapy for treatment of Hodgkin's lymphoma                  |
| AMH    | Anti-Müllerian hormone  |
| ART    | Assisted reproductive technologies                                |
| βhCG   | Human chorionic gonadotropin                                      |
| CI     | Confidence interval   |
| CNS    | Central nervous system  |
| CRN    | Cancer Registry of Norway   |
| FSH    | Follicle stimulating hormone                                      |
| GBC    | Gestational breast cancer   |
| GnRH   | Gonadotropin-releasing hormone                                    |
| HL     | Hodgkin's lymphoma  |
| HR     | Hazard ratio  |
| ICD-7  | International Classification of Disease, 7 <sup>th</sup> edition  |
| ICD-10 | International Classification of Disease, 10 <sup>th</sup> edition |
| ICSI   | Intra-cytoplasmic sperm injection (microinjection)                |
| IVF    | <i>In vitro</i> fertilisation                                     |
| LH     | Luteinising hormone   |
| LBW    | Low birth weight  |
| MBRN   | Medical Birth Registry of Norway                                  |
| N      | Number (of persons)   |
| NHL    | Non-Hodgkin lymphoma  |
| OR     | Odds ratio  |
| PABC   | Pregnancy-associated breast cancer                                |
| POF    | Premature ovarian failure   |
| REK    | Regional Ethical Committee  |
| RPLND  | Retroperitoneal lymph node dissection                             |
| SD     | Standard deviation  |
| SHBG   | Sex hormone-binding globulin                                      |
| SSB    | Statistics Norway   |

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## Publications included

- I. Stensheim H, Cvancarova M, Møller B, Fosså SD. Pregnancy after adolescent and adult cancer: a population-based matched cohort study. *International Journal of Cancer* 2011; Sep 1;129(5):1225-1236.
- II. Stensheim H, Klungsoyr K, Skjærven R, Grotmol T, Fosså SD. Birth outcomes among offspring of adult cancer survivors: a population-based study. *International Journal of Cancer* 2013; Dec 1;133(11):2696-705.
- III. Stensheim H, Møller B, van Dijk T, Fosså SD. Cause-specific survival in women diagnosed with cancer during pregnancy or lactation. A registry-based cohort study. *Journal of Clinical Oncology* 2009; Jan 1;27(1):45-51.



# BACKGROUND

## Introduction

This thesis investigates pregnancy rates after adolescent and adult onset cancer for both genders (paper I), birth outcomes in offspring born after cancer in either of the parents (paper II), and cause-specific survival of females diagnosed with cancer during pregnancy or lactation period and for women with a previous cancer diagnosis and with subsequent pregnancies (paper III). The most frequent cancer types in the age group 16-49 years at diagnosis are selected and analyses are performed with comparison to controls from the general population.

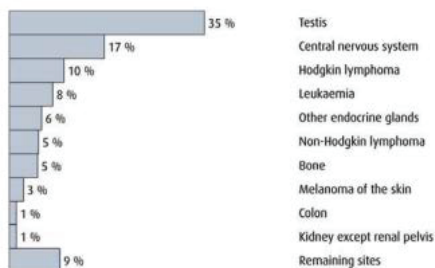
The growing number of cancer patients diagnosed in adolescence or in young adulthood, together with the increasing prognosis for many cancer types, makes it necessary to investigate the different long-term effects of cancer and its treatment. Concerning fertility and birth outcomes, most studies have focused on childhood cancer, and there has been a lack of studies based on large, unselected materials. Counselling young adult cancer patients about future fertility and the risk of adverse outcomes for the offspring is important, but large studies are needed to provide evidence-based advice. Further, counselling and care-taking of females being diagnosed with cancer during pregnancy are challenging. Again, research is needed to give evidence-based advice. When the study started in 2006, there were few large studies covering more than one cancer type. Case-reports provide more detail, but the statistics from population-based studies are crucial in questions of incidence and for reliable estimates of prognosis.

In 2005, a paper was published based on material from the Norwegian Radium Hospital, showing that fertility rates for former cancer patients were lower than among the general population, and that female cancer patients had lower fertility rates than male patients.<sup>1</sup> Further, the authors found elevated risks of congenital anomalies among the offspring of male cancer survivors.<sup>2</sup> There was a need for further investigation in a nationwide material.

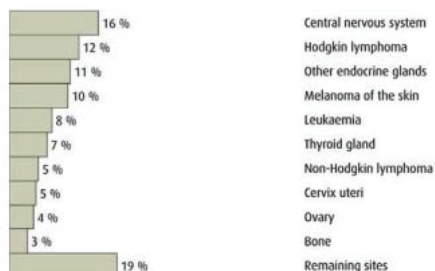
## Cancer epidemiology

For the Norwegian population during 2010, more than 27,000 individuals were diagnosed with a malignancy. The vast majority were aged over 50 years, but about 8% of the males and 14% of the females were between 15 and 49 years of age at diagnosis.<sup>3</sup>

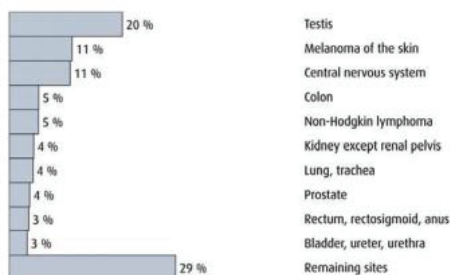
### MALES 15-24 years (551 cases)



### FEMALE 15-24 years (463 cases)



### MALES 25-49 years (5 337 cases)



### FEMALE 25-49 years (8 550 cases)

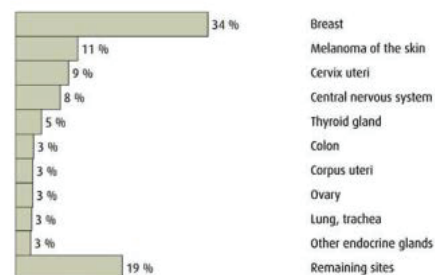
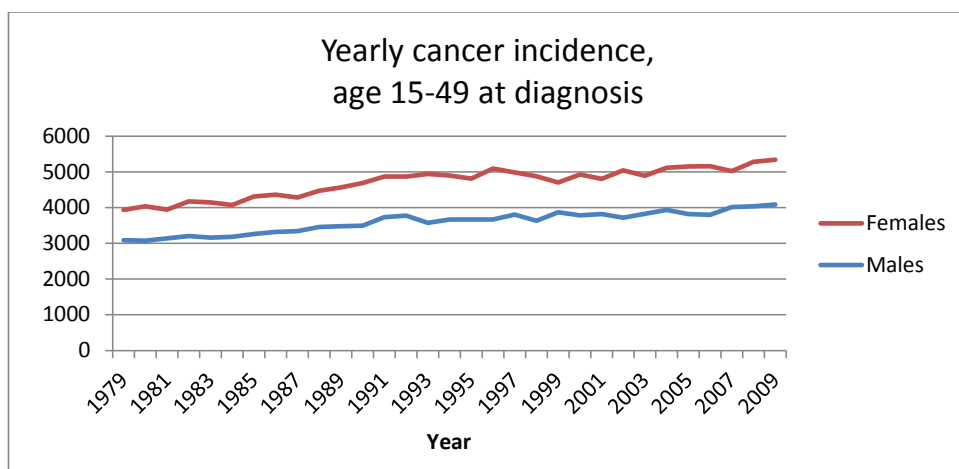


Figure 1

The most frequent incident cancer by age and gender, 2006-2010. Part of figure 5 from *Cancer in Norway 2010*.<sup>3</sup>

Figure 1 shows the incidence of cancer and the most frequent cancer types in adolescence and young adulthood. The cancer incidence has, in general, been increasing, also in younger age groups (Figure 2), and one out of three individuals in Norway is expected to be diagnosed with cancer before age 75.<sup>3</sup>



**Figure 2**

*Number of persons diagnosed with cancer at age 15-49 years in Norway per year during a period of three decades. Extracted from "Cancer in Norway" for the actual years.*

Cancer is the main disease-related cause of death for both genders in the age group 15-49 years old.<sup>4</sup> The prevalence, i.e. the number of survivors in the population who are alive and have been diagnosed with cancer, has increased over the last decades as the prognosis has improved for several cancer types (*Table 1*).

**Table 1**

*Prevalence of cancer, both genders, from The Cancer Registry of Norway*

| Year | Total no. of cancer survivors | Years after diagnosis |        |        |        |
|------|-------------------------------|-----------------------|--------|--------|--------|
|      |                               | <1                    | 1-4    | 5-9    | 10+    |
| 1980 | 71,880                        | 10,526                | 24,460 | 16,589 | 20,305 |
| 1990 | 103,659                       | 12,796                | 31,130 | 23,862 | 35,871 |
| 2000 | 143,410                       | 16,063                | 43,009 | 32,073 | 52,265 |
| 2010 | 207,224                       | 20,237                | 60,778 | 48,717 | 77,492 |

## Cancer survivorship

The term “cancer survivor” was introduced in the literature during the 1980s.<sup>5</sup> Cancer survivors were originally limited to individuals who had survived for five years or more after their diagnosis. Today, we often call them long-term survivors. The expression cancer survivor is nowadays often used for “someone who has had cancer”, and includes everyone once diagnosed with cancer who is alive, independent of the period of time since diagnosis. For this thesis, this recent definition will be used, and the terms cancer patient and cancer survivor will be used interchangeably. In contrast, there are examples in the literature of an extended use of the expression cancer survivor, including the cancer patient’s spouse and remaining family.<sup>6</sup>

The number of cancer survivors throughout the world has increased over the last few decades. By the end of 2010 there were more than 207,000 persons in Norway who had been previously diagnosed with cancer and were still alive. The majority (about 126,000) of those were diagnosed five years ago or more (*Table 1*).

The research into cancer survivorship has increased during the last two decades. The topic covers all types of long-term adverse effects, both physical and psychosocial, caused by the cancer and its treatment. Mapping adverse effects and trying to give advice and generate guidelines are of high importance, both for the individuals who have experienced cancer and are trying to resume life again, and for their caregivers. Also, cost estimates of cancer survivorship care plans are a public health concern. Some guidelines have been published, but on the whole, except for follow-up care focusing on cancer recurrence, care plans for managing the long-term effects of cancer and its treatment are lacking.<sup>7;8</sup>

The National Resource Centre for Late Effects after Cancer Treatment at the cancer clinic at Rikshospitalet was established in 2005, initiated by the Norwegian Ministry of Health and Care Services to meet the needs of the increasing cancer survivor population, their care givers and the societies handling the special questions raised.<sup>9</sup> The Resource Centre has published papers on a diversity of childhood and adult cancer survivorship topics, as specific treatment-related adverse effects, fertility, fatigue, impaired physical function, sick leave and work ability, increased morbidity, and second cancers.<sup>1;10-21</sup>

## **Long-term effects of cancer and its treatment**

Most cancer treatments lead to adverse effects, often grouped into acute, late, and long-term sequelae.<sup>22</sup> Acute effects are limited to the period of treatment and roughly one year afterwards, and longer lasting adverse effects are classified as long-term. Late adverse effects are those with a late debut, more than a year after treatment. Adverse effects are caused by the disease and the treatment. Individual factors, such as genetics and lifestyle, are of importance for the type and degree of sequelae. Sequelae such as cardiovascular disease or second cancer might be severe, or even life-threatening.

Being diagnosed with a potentially life-threatening disease might have both physical and psychosocial consequences. The psychosocial consequences of cancer and/or its treatment might include depression, anxiety, sleep-disorders, fatigue, and fear of relapse. Both the physical and mental consequences of cancer can lead to difficulties in daily life, influencing physical ability, employment, income, family life, and social behaviour.

There are effects caused by the cancer diagnosis and its treatment that are likely to influence the choice and ability of future parenthood. Morbidity like heart failure, reduced lung or kidney function, neurological problems, disabilities, or psychosocial factors, as mentioned above, might influence different parts of life, including fertility. For the remainder of this section, I will mainly focus on reduced fertility after cancer due to sequelae, not specifically categorised as acute or long-term sequelae, since both could be present. Morbidity which secondarily is likely to influence fertility or family-building are not estimated in the analyses.

In this thesis, reproduction after cancer is one of the main outcomes measured by comparing cancer survivors and age-matched controls without a history of cancer. Research has shown that at least some cancer survivors have reduced fertility.<sup>1;2;23;24</sup> Additionally, female survivors of breast cancer or brain tumours have slightly lower marriage rates compared with their cancer-free counterparts,<sup>25</sup> and survivors of testicular and cervical cancer tend to get divorced more often than the general population.<sup>26</sup>

## Cancer and fertility

The term fertility is often defined as the actual number of children one has, while fecundity is the potential reproductive ability (to conceive and give birth to live children). Fertility, reproduction after cancer, and parenthood are used interchangeably in this thesis, meaning the number of conceptions leading to registered pregnancies, as a measure of the ability to conceive, with or without assisted reproductive technologies. Infertility is usually defined as not getting pregnant in spite of unprotected intercourse for one year or longer. For cancer survivors, one year might be too short a period, which will be further discussed below.

Delay of childbearing to the late twenties or the early thirties has become usual in the western world in the last few decades. In Norway, the mean maternal age at first birth in 1967 was 22.6 (SD 4.3), whereas forty years later it was 27.5 (SD 5.1).<sup>27</sup> An increasing incidence of cancer combined with a delay of childbearing will necessitate the medical community's increased awareness of problems related to cancer and fertility.

Both the cancer itself and the treatment might lead to subfertility or infertility, of temporary or permanent duration. Besides physical sequelae, cancer might have an influence on social and intimate relations.<sup>25</sup> Cancer survivors might fear disease recurrence if getting pregnant, or fear of transferring cancer or other adverse conditions to the offspring<sup>28</sup>, which will interfere with family building after cancer. On the other hand, literature focusing on the psychosocial effects of cancer confirms the strong desire to have children, and the distress that infertility brings.<sup>28;29</sup> Several initiatives to preserve fertility have been established during the last decades, to improve the post-treatment options for cancer survivors. This will be dealt with in this chapter, first with a closer look at male and female gametogenesis, cancer treatment effects, methods to avoid gonadotoxicity, and further about methods to preserve fertility if the treatment is potentially gonadotoxic.

### Gametogenesis

Spermatogenesis starts in puberty with the continuous production of mature sperm cells. The complete process lasts about 70 days with different phases, and more than 100 million sperm cells are produced every day.<sup>30</sup> Primary germ cells formed in embryonic life undergo several divisions and finally become motile sperm cells. Spermatogenesis is regulated by luteinising hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland.

In the testicle, the germ cells are surrounded by Sertoli cells, which provide a protective matrix and nutrition for the germ cells, and Leydig cells, which produce testosterone following stimulation by LH. Testosterone is necessary for spermatogenesis; it gives feedback to the hypothalamus-pituitary axis, and is responsible for male body characteristics.

A female foetus with gestational age of 20 weeks has 7-8 million oocytes in her ovaries. At birth, the number is about 1 million in each ovary, but at puberty, caused by apoptosis, this number will have decreased to about 400 000. At menopause, only 400-1000 follicles remain. In each menstrual cycle, usually only one oocyte is released by ovulation, but a dozen or more are consumed each month during this process. Ovarian atresia accelerates after the age of 35. As with spermatogenesis in males, the menstrual cycle and ovulation are stimulated by LH and FSH.<sup>31</sup>

### **Chemotherapy and fertility**

Cytotoxic drugs interfere in the cell division cycle, and rapidly dividing cells like germ cells are the most susceptible. The gonadotoxic risk profile caused by chemotherapy is described in *Table 2*. Most gonadotoxic agents threaten both male and female fertility. Alkylating agents (especially cyclophosphamide) and procarbazine are probably the agents with highest risk to cause infertility. The drugs induce an impairment of follicular maturation and a depletion of primordial follicles in the ovaries. Alkylating agents also damage the steroid-producing granulosa cells. In the testicles, both spermatogonia, Leydig cells and Sertoli cells are attacked, leading to disrupted spermatogenesis, but Leydig cells are less sensitive, and testosterone production is usually maintained.<sup>32</sup> The level of gonadotoxicity caused by the cytostatic drugs is dependent on treatment type, combination, total dose, age at treatment (especially for females), and individual vulnerability, such as genetic factors and pre-treatment reserve. Apart from risk classification (*Table 2*) and age at treatment, we are still unable to accurately predict using current diagnostic tools who will be more vulnerable to chemotherapy than others.

Table 2.

Gonadotoxic risks for female and male patients, risk assessment based on type (and dose) of treatment. Abbreviations are described in the footnote.

|                             | High risk   | Intermediate risk  | Low risk  | Unknown risk  |
|-----------------------------|---|--|---|---|
| Chemotherapy, single agents | Cyclophosphamide<br>Busulfan<br>Melphalan<br>Chlorambucil<br>Dacarbazine<br>Procarbazine<br>Ifosfamide<br>Thiotepa<br>Cisplatin $\geq 500\text{mg/m}^2$ * | Anthracyclines<br>Cisplatin<br><400 mg/m <sup>2</sup> *<br>Carboplatin | Methotrexate<br>Bleomycin<br>5-Fluouracil<br>Actinomycin-D<br>Vinca alkaloids<br>Mercaptopurine<br>Etoposide<br>Fludarabine | Taxanes<br>Oxaliplatin<br>Irinotecan<br>Monoclonal antibodies<br>Tyrosine kinase inhibitors |
| Chemotherapy, combinations  | High-dose cyclophosphamide/ busulfan and hematopoietic stem cell transplantation. BEACOPP, CMF, CAF, FEC x 6 in women > 40 years                          | CMF, CAF, FEC x 6 in women 30-39 years. AC, EC x 4 in women > 40 years | ABVD<br>CMF, CAF, FEC x 6 in women <30 years. CHOP, CVP<br>AC in women < 40 years   |   |

Footnote: ABVD: doxorubicin (originally *adriamycin*), bleomycin, vinblastine, and dacarbazine; AC: doxorubicin and cyclophosphamide; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; CAF: cyclophosphamide, doxorubicin, and 5-fluouracil; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; CMF: cyclophosphamide, methotrexate, and 5-fluouracil; CVP: cisplatin, vinblastine, and prednisolone; EC: epirubicin and cyclophosphamide; FEC: 5-fluouracil, epirubicin, and cyclophosphamide.

\*Cumulative doses. Adapted from <sup>33;34</sup>

Male spermatogenesis has the ability to recover, if stem cells have survived. Recovery is seen over a period of one to five years after gonadotoxic treatment for many male survivors.<sup>35;36</sup> For females, gonadotoxic chemotherapy may reduce the total number of oocytes or accelerate the physiologic loss, leading to premature ovarian failure (POF, early menopause). Irreversible amenorrhoea, lasting more than 12 months and with raised FSH levels before the age of 40, is regarded as POF. Ovarian damage is dependent on the type of drug, total dose, and individual factors, especially age at the time of treatment. Risk of ovarian failure is highest among women closest to natural menopause, who have smaller follicular reserves. Even drugs classified as intermediate or low gonadotoxic treatment increase the risk of POF, even when normal menstrual cycles had been regained in the meantime.<sup>32</sup>



For some cancer types, changes in chemotherapy during the last decades have offered less gonadotoxic chemotherapy. An example of this is the change from combinations containing procarbazine to ABVD for Hodgkin's lymphoma patients, which has increased fertility after treatment in both genders.<sup>13;32;35;37</sup>

### **Radiotherapy and fertility**

Irradiation is a fertility threat if the reproductive organs are included in the field or hit by scattered irradiation (deviated rays from the straight beam). Besides the general effects which radiotherapy might cause, such as fibrosis and reduced vascularisation, the gonads themselves are sensitive to irradiation, and high doses imply infertility. Sperm concentrations usually reach a nadir 4-6 months after irradiation, and time to recovery is dose-dependent. It is reported that recovery to pre-irradiative sperm concentrations for a single dose of 1 Gy can be seen after 9-18 months, and that  $\geq 4$  Gy to the testes requires  $\geq 5$  years.<sup>38</sup> Fractionated treatment tends to give longer recovery times than single-dose treatment. Temporary arrest of spermatogenesis with recovery within 12-30 months is reported after scattered irradiation from abdominal fields with total doses from 0.2-0.9 Gy.<sup>31;39</sup> For females, scattered irradiation could result in ovarian dysfunction with doses  $< 0.1$  Gy to the ovaries, at least if the woman is above 40 years old. For younger females, the tolerance is higher, as total doses of at least 4-6 Gy are needed to induce permanent ovarian failure.<sup>31</sup> To limit irradiation of the gonads, lead shielding is used to avoid gonadotoxic doses. Oophoropexy, surgical removal of the ovaries outside the radiation field, is sometimes used, but the vascularisation of the ovaries might be disturbed and the success rate is modest.<sup>40</sup>

A secondary fertility-decreasing effect may occur if the brain is irradiated, including the hypothalamus and the pituitary gland, which will influence the menstrual cycle or the stimulation of spermatogenesis, by disturbing the production of FSH and LH.

For premenopausal breast cancer patients diagnosed prior to the 1980s, ovarian irradiation in absolute ovariotoxic doses (10-12 Gy) was used as an anti-hormonal treatment with a gradual substitution to tamoxifen during the 1980s.<sup>41;42</sup>

## **Surgery and fertility**

Removing the reproductive organs by surgery, like bilateral orchiectomy in males and hysterectomy or bilateral oophorectomy in females, obviously leads to infertility. Unilateral oophorectomy or orchiectomy will preserve fertility, but the remaining fertility will be dependent on the functional status of the contralateral organ. Gynaecological cancers in premenopausal women stand in an exceptional position with regards to reduced fertility after cancer treatment. Action to preserve fertility has been taken since the 1970s, by offering conisation to selected patients with cervical cancer of stage Ia (microinvasive disease).<sup>43</sup> Radical trachelectomy, which was introduced by Dargent and colleagues in the late 1980s, has been used as a fertility-preserving alternative since 1992. This method has also been used for women with stage Ib1 tumours < 2 cm and without risk factors, in combination with pelvic lymphadenectomy.<sup>44;45</sup> Furthermore, ovarian cancer patients with low stage disease have, since the 1980s, been given the option of unilateral oophorectomy, eventually followed by hysterectomy and oophorectomy after giving birth to the desired number of children.<sup>45;46</sup>

Surgery close to the reproductive organs, like pelvic and retroperitoneal operations, might influence the vascular beds and disturb nerve functions, and thus influence sexual life (leading to sexual dysfunction), secondarily reducing fertility, or the capability to bear a pregnancy to term.<sup>47</sup> Retroperitoneal lymph node dissection (RPLND) is an example of surgery leading to nerve dysfunction, which was used in Norway from the 1980s onwards in testicular cancer patients both for diagnostic and treatment purposes. During the first five years, bilateral RPLND was most frequently used, resulting in nerve damage and dry ejaculation. In the late 1980s, unilateral and nerve-sparing procedures were introduced to improve fertility preservation, resulting in a reduction of men with post-operative ejaculatory dysfunction from 90% to 10%.<sup>48;49</sup> Also, brain surgery, involving the hypothalamus and the pituitary gland, will influence sperm production and the ovulation cycle negatively.

## **Cancer as a cause of decreased fertility**

It has been proposed that testicular cancer is linked to subfertility,<sup>50</sup> and Hodgkin's lymphoma has also been associated with decreased fertility evaluated at diagnosis.<sup>51</sup> Hypospadias (a birth defect; abnormally placed urethra opening) and cryptorchidism (an

undescended testicle) are both associated with an increased risk of testicular cancer.<sup>52</sup> It has been postulated that poor semen quality (low sperm count), hypospadias, cryptorchidism, and testicular cancer all are symptoms of one underlying entity, called testicular dysgenesis syndrome (TDS). This syndrome is linked to development of the gonads in foetal life.<sup>52</sup> The production of  $\beta$ hCG by some histological subtypes of testicular cancer is also regarded to have a negative effect on semen quality. Patients diagnosed with testicular cancer, with or without TDS, are often reported to have impaired spermatogenesis at diagnosis, meaning that the remaining testicle could also be involved.<sup>50</sup>

In males with Hodgkin's lymphoma, low sperm counts (oligospermia or azoospermia; few or no sperm cells in a semen sample) are reported prior to treatment for up to 70% of patients<sup>53;54</sup> in some studies, while others did not find any large decline in semen quality.<sup>55</sup> The mechanisms are not fully understood, but are hypothesised to be linked to immune-mediated processes with the increased release of pro-inflammatory cytokines.<sup>55</sup> A difference associated to stage has also been shown. Low sperm counts at diagnosis are most likely associated with advanced stage and the presence of systemic effects of the cancer (B-symptoms; fever, night sweats, weight loss), in particular fever and night sweats.<sup>32;51;53</sup> Nevertheless, the decreased fertility before treatment seems to be temporary, with recovery reported for most survivors.

## Fertility-preserving options prior to treatment

### **Semen cryopreservation**

The first sperm bank in Norway, St. Olavs Hospital in Trondheim, opened in 1980, and the second in 1994, at Rikshospitalet in Oslo. Today, there are sperm banks also in Tromsø, Porsgrunn, Haugesund, and Bergen. Any sample with living sperm cells is frozen, and post-pubertal men up to the age of 55 are given this option nowadays. However, it is reported that a low proportion of cancer survivors, only 7% of testicular cancer patients with semen cryopreservation prior to treatment, are using their samples to conceive after their treatment, with a success rate of about 50%.<sup>11</sup>

## **ART (Assisted reproductive technologies)**

Most ART procedures include hormonal hyperstimulation of the ovaries and harvesting of multiple oocytes. IVF, *in vitro* fertilisation, has been possible in Norway since 1989 and uses a number of motile sperm cells for the fertilisation of oocytes in a culture medium. IVF is performed mainly in the case of female factor subfertility and in cases of sperm donation (oocyte donation is not legalized in Norway).<sup>56</sup> Intra-cytoplasmic sperm injection (ICSI, also called microinjection) has been used since 1995. One selected sperm cell is injected into the oocyte directly. This technique is frequently used today and always if there is male factor of subfertility.

## **Embryo and oocyte cryopreservation**

Oocyte and embryo cryopreservation requires hormonal stimulation and therefore usually a delay in treatment of 2-6 weeks. A new method with hormonal stimulation starting independently of the cyclic phase is able to reduce the time before harvesting, and the methods might then become a more realistic possibility for preserving fertility in cancer patients.<sup>57</sup> Oocytes are harvested during ovulation, and IVF is performed in the case of embryo storage. In Norway, embryo cryopreservation requires a partner (marriage or cohabitate relation for at least two years). Oocyte cryopreservation is a possibility for single women, but oocytes are less robust to the freezing process than embryos, and the method is still considered experimental. Few women with cancer worldwide and in Norway have used embryo or oocyte cryopreservation.<sup>58</sup>

## **Ovarian tissue cryopreservation**

For females needing high gonadotoxic chemotherapy or abdominal-pelvic irradiation which includes the ovaries, ovarian tissue cryopreservation might be the only option to preserve the possibility of getting pregnant after cancer. The technique is still considered experimental, but has been allowed in Norway since 2004. About 130 females have used this opportunity (as of ultimo 2012) and two autotransplantations have been performed in Norway (Tom Tanbo, personal communication). There is no lower age limit, and the method is the only possibility for pre-pubertal girls. The upper age limit for harvesting is 35 years. Storage time is unlimited, but autotransplantation should optimally be performed before the age of 40, and the woman should have been cancer-free for at least 5 years. If a spontaneous pregnancy is not achieved in a set number months, hormonal stimulation is

employed to induce ovulation.<sup>59</sup> By now, approximately 20 children have been born by means of this technique worldwide.<sup>60</sup>

### **Measuring post-treatment fertility potential**

Both male and female survivors might have apparent infertility for a period after treatment. Additionally, to minimise the risk of birth defects and other complications, the general advice to survivors who want to get pregnant after cancer is to delay conception for at least a year after the treatment has ended. The possible temporary sub- or infertility might last for some years.

Today, we have several techniques available to estimate fertility potential. For males, sperm samples will show whether the concentration, morphology and motility are sufficient to fertilise an oocyte. A temporary subfertility or even infertility is described initially, and the recovery of sperm quality is seen during the first two-three years after treatment, classified as medium or even high gonadotoxic risk chemotherapy (*Table 2*).<sup>10;33;61</sup> Furthermore, hormones (FSH, LH, SHBG, and testosterone) regulating sperm production need to be evaluated. Elevated FSH might represent exocrine hypogonadism, and low testosterone and/or elevated LH could represent endocrine hypogonadism.

For females, regular menses are not necessarily reliable evidence of preserved or regained fertility, as anovulatory cycles are possible. Oocyte reserves can be measured with ultrasound, assessing the number of antral follicles and the volume of the ovaries. Further, serum levels of different hormones are measured (FSH, LH, E2 (oestradiol), anti-Müllerian hormone (AMH), and inhibin B); the hormonal levels will indicate whether the woman has signs of gonadal dysfunction or is threatened by premature ovarian failure and early menopause. AMH is considered to be independent of the menstrual cycle (in contrast to the other hormones listed above), and reflects the number of follicles in the gonads.<sup>61</sup> In healthy women, AMH values decrease with increasing age, which is further accelerated after gonadotoxic treatment. AMH might also be used as a pre-treatment prediction of fertility, but this is still experimental.

## Pregnancy after adolescent and adult cancer

For young adult and adolescent cancer patients, facing a future without children might represent an extra burden and have a negative influence on quality of life. Fertility-preserving attempts have been included in the guidelines for several cancer types, as described earlier for gynaecological cancer of low stage<sup>45</sup> and Hodgkin's lymphoma.<sup>62</sup> However, for other malignant diagnoses, like acute leukaemia, more intensive treatment and highly gonadotoxic chemotherapy is required to cure the cancer, which unfortunately also is a real threat to their fertility.<sup>63;64</sup>

Surveys show that many young adult cancer survivors want to have children after cancer, but they are concerned about a pregnancy's influence on their own health and about the cancer treatment's influence on the offspring's health.<sup>10;13;28;29</sup> In the past, poor prognosis might have led to low fertility rates after cancer, for example in those diagnosed with leukaemia. Most studies report lower fertility-rates among cancer survivors than among controls.<sup>2;65-67</sup> Besides, for female survivors, historic counselling often recommended either no future pregnancies, or at least a longer recurrence-free period (at least five years) before attempting pregnancy.

The literature at the onset of this thesis consisted mainly of studies about spermatogenesis or amenorrhoea after cancer treatment,<sup>53</sup> and about fertility after cancer in childhood or adolescence.<sup>68</sup> Regarding parenthood in adult cancer survivors, a single-institution study from The Norwegian Radium Hospital showed a 10-year cumulative probability of having a child after cancer in 14% in cancer survivors aged 15-45 years at diagnosis.<sup>1</sup> Further, for selected cancer types, like testicular cancer, Brydøy *et al.* reported an overall paternity rate of 71% during the first 15 years after cancer diagnosis, with a range from 48-92% in the high-dose chemotherapy group compared to the surveillance group.<sup>10</sup>

## Birth outcomes in the offspring of cancer survivors

Several studies have been published assessing the risk of adverse birth outcomes among childhood cancer survivors.<sup>69-71</sup> For this topic, case-reports and mono-institutional studies are more frequent than population-based studies, with the risk of selection bias. The main factors analysed are low birth weight, preterm birth, perinatal death and congenital

anomalies; other parameters have also been assessed, such as sex ratio, and factors associated with maternal health, all of which might influence foetal development and wellbeing.

### **Congenital anomalies**

Major congenital anomalies occur in 3-4% of all pregnancies in the general population.<sup>27;56</sup> Congenital anomalies are of different severity, and not all are detected during the first examinations of the newborn, which are those registered in the MBRN. When taking into account those birth defects presenting later in life, the incidence is at least twice these figures. The most vulnerable time in pregnancy is during organogenesis (the period when all organs are developed), i.e. the first 8 weeks after conception.

Chemotherapy might have teratogenic effects and increase the risk of foetal death, abortions, and major malformations, if given during pregnancy, and especially in the first trimester.<sup>72</sup> Both patients and health workers have been worried about whether pregnancy after cancer is associated with increased health risks for the offspring. However, reassuring results regarding chromosomal abnormalities among the offspring of childhood cancer survivors in comparison to cancer-free siblings and their offspring can be found in a population-based Danish study.<sup>73</sup>

A Norwegian mono-institutional study found a higher risk of fathering a child with malformations among selected male survivors, compared to controls, for all cancer types combined. The increased risk was only seen in the first child fathered by the survivors after cancer, and no such risk was observed among offspring of female survivors.<sup>2</sup> Three Danish studies covering female survivors of breast cancer, malignant melanoma, and Hodgkin's lymphoma did not find an increased risk of congenital anomalies among the offspring.<sup>74-76</sup> A Swedish study covering breast cancer, which found contrasting results to those of the Danish study, observed a higher incidence of congenital anomalies among the offspring of survivors compared to their controls, and with a time trend pointing to an increased risk of the most recent period.<sup>77</sup>

## **Perinatal death**

Stillbirth and infant mortality, often described as perinatal death, is one of the most severe adverse pregnancy outcomes, together with major malformations. Perinatal death has different definitions in the literature. Stillbirth is defined as the death of a foetus with a reasonable chance of survival outside the uterus, usually from the 28th gestational week. In this thesis, the cut off is set at 22 weeks, which is more frequently used nowadays.<sup>56</sup> Further, a birth weight criterion of at least 500 g is added. The limits are given to exclude early stillbirths, where the underreporting might bias the analysis. Perinatal death includes the period before and during the delivery, and the first 7 days after delivery. The rates of perinatal mortality in the general population are low in Norway and Nordic countries. The rate of perinatal mortality has declined from 23.3/1000 births in 1967 to 5.8/1000 births in 2006.<sup>27</sup> The risk of perinatal death is, in general, increased with advanced maternal age, multiparity, maternal complications during pregnancy, maternal smoking, and obesity. For offspring of cancer survivors diagnosed during adolescence and adulthood, no increased risk of perinatal death is reported from larger studies,<sup>75-77</sup> except for the first-borns of female cancer survivors who were childless at diagnosis (all cancer types seen together).<sup>2</sup>

## **Other adverse pregnancy outcomes**

Birth weight is linked to gestational age, and is a difficult outcome to measure. The condition that should be measured is intrauterine growth retardation, which is usually measured either by assessing small for gestational age or by dichotomising low birth weight (LBW) at term (<2,500 g at  $\geq 37$  weeks of gestation).<sup>56</sup> LBW at term has been reported from several studies about birth outcome in adult female cancer survivors.<sup>2;77;78</sup>

Preterm birth or prematurity is associated with higher risks of perinatal death, since the development for extra-uterine life not is fulfilled. Preterm birth for cancer survivors might be caused by a dysfunctional cervix or insufficient development of the placenta. An increased risk of preterm birth is reported for female cancer survivors who were pregnant after cancer.<sup>2;78;79</sup>



## Survival in females with pregnancy-associated cancer

Approximately 1 per 1000 pregnant women will be diagnosed with cancer during pregnancy.<sup>80,81</sup> The expression pregnancy-associated cancer is commonly used for breast cancer (see below), but also for other cancer types detected during pregnancy, or the first period after, usually the first year post-partum. The following paragraphs will deal with cancer diagnosed during or shortly after pregnancy, and the effect of subsequent pregnancies on cancer survival.

Pregnancy-associated cancer is a challenging situation for all involved, not only for the woman, her partner and their extended family, but also for health workers. Diagnostic procedures and treatment might harm the foetus, and making exceptions from the standard diagnostic and treatment procedures might be a threat to the mother's health and prognosis, resulting in a delay in diagnosis and/or suboptimal treatment. A multi-disciplinary approach is necessary to optimise the situation for the mother and the unborn child.<sup>82</sup> In general, surgery is preferably performed during the second trimester if possible. Most chemotherapeutic agents can be given during the second and third trimester, even though most cytotoxic have low molecular weight, which cross the placenta and reach the foetus (antimetabolites are the most teratogenic agents and should probably be avoided). Abdominal shielding should be used when radiotherapy is given during pregnancy, and irradiation involving the abdomen and pelvis should be delayed until after delivery. For females diagnosed with cancer after delivery, there are no reasons for treatment delay, but there is an indication for weaning from breastfeeding in the case of chemotherapy.

The influence of pregnancy on cancer survival has long been a controversial issue, and has influenced the thinking and handling of cancer types like breast, ovarian, and endometrial cancer. Pregnancy implies physiological changes in endocrine and immunological systems. It has been hypothesised that increasing oestrogen (and progesterone) levels leads to rapid tumour growth and advanced disease with decreased survival.<sup>82</sup> Pregnancy and lactation change the mammary glands, and permanent changes in hormone levels after childbearing are reported. The immunological system is down-regulated during pregnancy, to avoid rejection of the foetus. What these changes during pregnancy mean for the development of a malignant tumour and its course is still unknown.

## Breast cancer

Breast cancer is the most common malignancy in women. The majority of women are diagnosed after menopause, but 5-10% is diagnosed before the age of 40.<sup>3;83</sup> Pregnancy-associated breast cancer (PABC) or gestational breast cancer (GBC) are common expressions in the literature, often including the first year post-partum. The reason why these expressions not only include pregnancy but also a period after, is that the tumour has developed during the pregnancy or even before, and has been exposed to the physiological changes caused by the pregnancy and the lactation period. The incidence of PABC is about 2% of all cases diagnosed with breast cancer, or 1 in 3,000 to 1 in 10,000 pregnancies.<sup>84;85</sup>

Historically, women with breast cancer diagnosed during pregnancy or lactation were classified as inoperable.<sup>86</sup> Breast cancer in young persons (below 30) was looked upon as very aggressive and with a poor prognosis, and this poor prognosis was further enhanced because of the hormonal stimulation and active metabolism during pregnancy and lactation. However, not all surgeons agreed with this view, but the notion that pregnancy termination was necessary to improve the prognosis was widespread. Basically, only those who terminated their pregnancy underwent mastectomy. With regard to subsequent pregnancies, it was considered safe if the patient had been radically treated.<sup>87</sup> Later on, a survey was conducted in the 1950s, where 55 physicians especially interested in breast cancer were invited to participate. The majority agreed that breast cancer diagnosed during pregnancy should not alone lead to renouncement from surgical treatment. Subsequent pregnancies should be avoided, but sterilisation was not necessary. The surgeons were concerned that residual tumour cells would be stimulated by a subsequent pregnancy, leading to disease in the remaining breast or to metastases. Regarding the termination of pregnancy, there were disagreements; some believed that termination would improve the prognosis, and suggested termination even in the third trimester, while a smaller group thought that termination was not favourable for the prognosis.<sup>88</sup>

In the 1970s, when the prognosis of breast cancer in general had improved, the attitudes towards PABC changed, and localised breast cancer during pregnancy was principally viewed as operable.<sup>89</sup> Primarily, women with node negative disease were advised to delay a subsequent pregnancy for at least three years after diagnosis. However, many premenopausal women with oestrogen receptor-positive (ER+) disease underwent castration by

surgery or irradiation to eliminate the influence of ovarian oestrogen. In Norway, breast cancer patients underwent castration up to the early 1980s.<sup>42;90</sup>

Several studies up to the 1990s found a poor outcome for women diagnosed during pregnancy.<sup>91;92</sup> Hypotheses regarding the observed aggressive outcome of PABC included explanations like hormonal changes, increased vascularisation, and other changes of the breast tissue which might enhance tumour growth..<sup>93;94</sup> Oestrogens are in general known to induce breast tissue growth.<sup>91;92;95</sup> In recent years, several publications have concluded that gestational breast cancer often is diagnosed in advanced stages. However, if stage is adjusted for, the prognosis is similar to females who were not pregnant when diagnosed.<sup>96</sup> The breasts in pregnant and lactating women are difficult to examine, both clinically, with ultrasonography, or with mammography. A lump might thus be masked by the overall firmness of the breast tissue, delaying the final diagnosis.<sup>82</sup> The incidence of PABC is described as lower than expected, but higher after pregnancy than during pregnancy, pointing to a possible diagnostic delay.<sup>97;98</sup>

Regarding pregnancies subsequent to breast cancer, Sankila *et al.* described the favourable survival for women having babies after breast cancer using an expression borrowed from cancer and work life, namely the “healthy mother effect”.<sup>99</sup> It underlines the selection of women who are cured of cancer and perceived healthy enough to initiate a pregnancy after their malignant diagnosis. The optimal time period between cancer diagnosis and a subsequent pregnancy is not fully investigated, and guidelines today are mostly based upon “common sense”, recommending waiting 2-3 years after diagnosis. An Australian group found improved overall survival in women who conceived at least 24 months after diagnosis (HR = 0.48, 95% CI 0.27 to 0.83).<sup>67</sup> Similar figures were seen in a Danish study.<sup>65;100</sup> Since a dual effect of pregnancy is seen on the lifetime risk of being diagnosed with breast cancer, with an initial increased incidence risk turning into a long-term decreased risk, it is crucial to give advice regarding how long to delay pregnancy after cancer.<sup>101;102</sup>

## **Malignant melanoma**

The incidence of malignant melanoma has been increasing for the last few decades. A new diagnosis of malignant melanoma complicates 0.1–2.8 per 1000 pregnancies. Of all gestational cancers, malignant melanoma is reported to account for 8% to 30%, thus being

one of the most common malignancies during pregnancy.<sup>82</sup> The numbers seem to vary geographically and also with skin type, with a higher incidence among the fair-skinned population in the world.

In 1951, Pack and Scharnagel published a paper presumably reflecting common notions of malignant melanoma diagnosed in association with a pregnancy at the time. They described 32 patients with pregnancy-associated malignant melanomas, and reported worse prognosis than expected for pregnant women.<sup>103</sup> There was no comparison group with non-pregnant women at the time of diagnosis; also, upon closer inspection, only 10 were actually pregnant when diagnosed. It is also unclear whether the pregnant women were offered the same treatment as non-pregnant women. Still, this publication may have been the main reason why doctors have regarded malignant melanoma during pregnancy as a prognostic negative factor for decades.

There have been several hypotheses regarding malignant melanoma and pregnancy; Katz *et al.* have listed the most common ones.<sup>104</sup> The notion that benign nevi may grow or change during pregnancy has been shown not to hold true. Regarding endogenous hormones and their possible influence on the risk of malignant melanoma, no association between ever having been pregnant and malignant melanoma risk is found.<sup>105</sup> Furthermore, higher parity (more than five) seems to be protective against developing malignant melanoma, but if this is related to parity, hormonal factors, or behaviour, are unclear.<sup>106</sup> Regarding exogenous hormones, oestrogen-containing oral contraceptives and hormonal replacement therapy have not been found to have any adverse effect with a greater risk of recurrence,<sup>107-110</sup> and are not contraindicated for women with a history of localised malignant melanoma.<sup>111</sup>

Tamoxifen has been used as a single agent or in combination with chemotherapy in the treatment of disseminated malignant melanoma. The medicine has been described as inducing apoptosis and inhibiting angiogenesis, through which tumour cell growth was suppressed.<sup>112</sup> However, meta-analyses have shown that Tamoxifen do not improve response or survival rates in malignant melanoma patients.<sup>112-114</sup> The rationale for introducing Tamoxifen in the treatment of melanoma was originally driven by a hormonal hypothesis, because of the observed oestrogen receptors in the tumour cells and studies

reporting oral contraceptives leading to progression. More recent immunohistochemical techniques have failed to prove the existence of oestrogen receptors.<sup>112</sup>

Regarding malignant melanoma diagnosed during pregnancy, recent population-based studies do not confirm the “hormonal hypothesis” related to malignant melanoma, nor the finding of worse survival for women diagnosed during pregnancy.<sup>115-117</sup> Initial tumour thickness seems to be the only important prognostic factor, possibly besides tumour site.<sup>110;115</sup> Treatment of early stage disease involves only localised surgery, and there is no reason for the postponement of such treatment during pregnancy.

### **Cervical cancer**

Cervical cancer is the most common gynaecologic malignancy associated with pregnancy, with an incidence of 1 in 1000 to 1 in 10,000 pregnancies.<sup>82;118</sup> The symptoms are usually discharge, occasional bleeding or post-coital bleeding, which could be confusing during pregnancy. Until the 1980s, pregnancy termination was suggested for females diagnosed during their first or second trimester.<sup>119</sup> In recent years, for females with early stage disease and no nodal involvement, pregnancy preservation is the aim. Vaginal examination with histological proof is necessary, while endocervical curettage is contraindicated. Complete excision by conisation might be performed by experienced teams during early pregnancy if invasive disease is suspected. The risks with conisation are bleeding, premature delivery, infection, and pregnancy loss. In cases where the cancer is detected at a later stage in the pregnancy, foetal maturity must be optimised followed by a planned early delivery and then cancer treatment.<sup>82;118</sup> Delay of treatment for stage I disease to allow foetal maturation is found to be safe, when followed by frequent examinations to detect eventual progression. Caesarean section is recommended to prevent recurrences in the episiotomy scar, and vaginal delivery is, in some studies, listed as a prognostic negative factor for recurrence.<sup>120;121</sup>

The prognosis for women with cervical cancer during pregnancy is equal to non-pregnant women with similar stage.<sup>121-124</sup> For females diagnosed with cervical cancer shortly after pregnancy, survival was found to be worse than for pregnant females with cervical cancer, and for controls who were not pregnant at the time of diagnosis. The two main risk factors were high stage and vaginal delivery.<sup>120</sup>

## **Ovarian cancer**

The incidence of ovarian tumours during pregnancy is reported to be about 1-4%, but the majority of these are masses of benign character. The average estimated incidence of malignant ovarian tumours in pregnancy is approximately 1 in 10,000 to 1 in 20,000 deliveries.<sup>82;125</sup> Also, the view regarding ovarian cancer associated with pregnancy has been influenced by a hormonal hypothesis, and historically, this might have led to reluctance regarding treatment. Epidemiologic evidence shows that the risk of ovarian cancer is decreased following childbirth and oral contraceptives also have a protective effect.<sup>126</sup> An ovarian tumour might be asymptomatic for a long period, but may become symptomatic during pregnancy when the uterus is enlarging, or may also represent a physical obstacle in the pelvis during delivery. The tumour might even be occasionally observed at the gestational routine ultrasonographic examination or during caesarean section,<sup>125;127</sup> Contrary to late diagnosis and poor prognosis, both of which are associated with ovarian cancer in general, pregnancy might in some cases lead to an early diagnosis. Diagnostics are mainly based on ultrasonography and clinical findings. The concentration of the ovarian cancer antigen 125 (CA-125) is described as higher than normal during the first trimester and postpartum, and can be misleading as a tumour marker in case of the detection of an ovarian mass.<sup>128</sup> Pelvic CT is contraindicated during pregnancy. Surgical intervention is indicated for persistent adnexal masses suspected as malignant, preferably during the second trimester.

Survival outcomes of pregnancy-associated ovarian cancer are not reported to be different from those among non-pregnant patients.<sup>127;129;130</sup> Treatment approach depends on tumour size, histological type, morphology, malignant potential, and term of pregnancy.

## **Lymphoma and leukaemia**

The diagnosis of malignant lymphoma is reported to complicate 1 in 6000 pregnancies, mainly Hodgkin's lymphoma (HL), as non-Hodgkin lymphoma (NHL) during pregnancy is very seldom reported.<sup>131</sup> Leukaemia is reported to occur in about 1 of 75,000-100,000 pregnancies.<sup>81;82;132</sup> The early incidence peak of HL is between 20 and 40 years of age, coincidentally with the childbearing years, while the mean age at diagnosis of NHL is 42. The influence of pregnancy on the course of HL has been controversial. In the 1950s, a

report concluded that survival was poorer for females diagnosed with HL during pregnancy.<sup>133</sup> However, from the 1960s onwards, several series concluded that survival was similar for pregnant and non-pregnant females with HL, and that therapeutic abortion did not improve the course or survival.<sup>134-136</sup> If diagnosed during pregnancy, the treatment of HL of low stage and indolent NHL might be safely delayed until after delivery, or at least until the second trimester.<sup>131;137-139</sup>

In the case of acute leukaemia, and aggressive NHL types, treatment must be started immediately, irrespective of gestational stage. The treatment represents a threat to the foetus, with a risk of miscarriage, intrauterine growth retardation, prematurity, and foetal death, but a delay will challenge maternal prognosis.<sup>140</sup> Case-reports have only been published about NHL<sup>139;141;142</sup> and leukaemia during pregnancy; for NHL, 103 cases were reported in 1994 over a period of 60 years,<sup>143</sup> and an additional 35 cases were reported by 2005.<sup>137</sup> Early diagnosis and proper treatment are necessary to obtain survival, as in non-pregnant patients. Termination of pregnancy is recommended for females diagnosed in the first trimester, since evidence regarding intensive combination treatment for NHL or leukaemia is limited. Termination is not indicated for maternal benefit if diagnosed at a later gestational stage. If acute leukaemia is diagnosed during the first trimester, termination of pregnancy is usually required, especially in the case of stem-cell transplantation, which is contraindicated during pregnancy. Standard multi-agent chemotherapy is associated with foetal growth restriction and myelosuppression. However, several case-reports refer to no foetal toxicity or other adverse birth outcomes.<sup>131;137;144;145</sup> There are reports of the successful modification of treatment with the exchange of dexamethasone to prednisone or methylprednisone because of foetal risk of neurologic sequelae, and exchange of methotrexate to arabinosylcytosine because of concerns over the potential toxic effect of methotrexate to trophoblastic cells.<sup>137</sup>

No association has been found between the incidence of NHL or leukaemia and pregnancy factors.<sup>146-148</sup> The literature of subsequent pregnancies is scarce, and again, based on case-reports.

## Brain tumours

The term “brain tumours” represents a diverse classification, as intracranial tumours of all histological types, from benign lipomas to aggressive malignancies like glioblastomas, are included. The malignant potential is dependent on the type of tumour, its location, its size and its state of development. The literature about brain tumours occurring during pregnancy and the lactation period is scarce, and made up of case-reports; incidence rates are variable, but a Spanish study reported numbers of about 5 malignant cases per 100,000 pregnancies and a German study reported 3.6 per 100,000.<sup>149-152</sup> As for other malignancies, there is a risk of diagnostic delay because the symptoms may be considered part of the common pregnancy conditions. Recent studies report no association between brain tumours and pregnancy,<sup>153;154</sup> while some older studies point to an increased risk of meningioma for those ever pregnant<sup>155;156</sup> Historically, hypotheses about hormonal changes causing an acceleration of growth during pregnancy were stated, and oestrogen and progesterone receptors are detected in brain tumours. The observation of enlarging meningiomas and neurinomas during pregnancy has often been explained by water retention and increased fluid content, supporting the observations of symptom onset during pregnancy and recovery after delivery.<sup>155;156</sup> In contrast to older reports, Haas *et al.* reported fewer than expected number of intracranial malignancies during pregnancy compared to the general population.<sup>152</sup> To my knowledge, survival rates have not been calculated for brain tumours in pregnant women compared to those of the non-pregnant population.

Hormonal changes after treatment are common, since the pituitary gland and hypothalamus are often involved in the brain tumour itself or its treatment. This means that fertility can be impaired, hormones of importance during pregnancy can be imbalanced, and the tumour itself could also have caused fertility problems prior to diagnosis. Outcomes for subsequent pregnancies are scarcely reported.

## Thyroid cancer

The incidence rate of thyroid cancer during pregnancy ranges from 3 to 14 per 100,000 live births.<sup>82;157</sup> Thyroid cancer is the most common endocrine tumour in young females in the general population. When diagnosed at a young age, the cancer usually has a non-aggressive histology related to a favourable prognosis. Females diagnosed during pregnancy have the same prognosis as non-pregnant patients, even though thyroid cancer during pregnancy may



grow faster since hormonal factors (hCG) could accelerate tumour progression, or maybe because of pregnancy-related immune tolerance.<sup>157;158</sup> In a normal pregnancy, hCG stimulates the thyroid gland and increases its volume and its hormone production. For the above-mentioned reasons, diagnostic delay of gestational thyroid cancer is likely, and more advanced stages are often seen in pregnant women compared to non-pregnant women.<sup>82</sup>

Besides the challenge of handling thyroid cancer during pregnancy, the second challenge regarding this disease is to reach an adequate hormonal balance in the pregnant survivors after thyroid cancer using thyroxin substitution. Maternal supply of thyroid hormones is crucial for the normal development of the foetal brain, especially during the first trimester. Severe neurological disorder, miscarriage or foetal death can be the result of maternal hypothyroidism.<sup>82</sup>



## STUDY AIMS

The principal aims of this project were to study the impact of cancer on fertility and on pregnancy outcomes after cancer in a population-based material. We also wanted to compare survival in females who had subsequent pregnancies or were diagnosed with cancer during pregnancy or the lactation period with survival in females without pregnancy-associated cancer. We wanted to validate findings from the previous literature regarding these subjects. Based on the literature described in the introduction chapter, there is a lack of large, unselected, controlled materials investigating the following questions, and the findings are contradictory for several of the outcomes. The growing incidence of cancer among adolescents and young adults and of cancer during pregnancy emphasises the need of evidence-based knowledge, as far as such can be reached.

In detail, the following research questions were defined:

- |           |   |  |
|-----------|---|--|
| Paper I   | { | <ul style="list-style-type: none"><li>• Are pregnancy rates after cancer lower than in the general population?</li><li>• Are there differences in pregnancy rates regarding cancer type and treatment?</li><li>• Do male cancer survivors have higher fertility rates than female survivors?</li><li>• Have fertility-preserving cancer treatments resulted in increased fertility-rates after cancer for selected cancer types?</li></ul> |
| Paper II  | { | <ul style="list-style-type: none"><li>• Are congenital anomaly rates in offspring of male cancer survivors higher than those in the general population?</li><li>• Are adverse pregnancy outcomes like perinatal death, preterm birth and low birth weight more frequently seen in infants delivered by female cancer survivors than in offspring of females without a previous cancer diagnosis?</li></ul>                                 |
| Paper III | { | <ul style="list-style-type: none"><li>• What is the incidence of pregnancy-associated cancer?</li><li>• Is survival for females diagnosed with a pregnancy-associated cancer poorer than for non-pregnant or non-lactating females with cancer, assessed for all and for selected cancer types?</li><li>• Do female survivors with subsequent pregnancies have poorer survival than those not becoming pregnant after cancer?</li></ul>    |



# MATERIALS AND METHODS

## Data sources

This is a population-based study with material from different national data sources. The Cancer Registry and the Medical Birth Registry of Norway were the main data sources for identifying cases and for outcome and explanatory variables.

From 1964, all citizens in Norway have been given a unique personal identification number with 11 digits. It is called the birth number, and is composed of the date of birth, a three digit individual number, and two check digits. Since the 1960s, all inhabitants have been given such an identification number shortly after birth. This number enables personal information from different sources to be linked.

## Cancer Registry of Norway (CRN)

The CRN provides close to complete incidence data on all individuals diagnosed with cancer in Norway since 1953.<sup>159</sup> The reporting is mandatory, initiated by a directive from the Ministry of Health and Social Affairs in 1951. The reporting is based on pathology and cytology reports, clinical records, and death certificates. Variables like cancer site, date of diagnosis, histological type, basis for the diagnosis, stage or extent of the disease, and initial treatment in broad terms (for the first four months) are reported.

Within the CRN, extent of disease is described as localised, regional spread, distant spread or unknown for most solid cancer types. Cervical cancer is categorised as stage of disease from I-IV, according to the Federation Internationale de Gynecologie et d'Obstetrique (FIGO). Similarly, breast cancer is classified as localised tumours (I), regional lymph node metastases (II), direct tumour extension to the chest wall or skin (III), or distant metastases (IV). Brain tumours include all benign and malignant intracerebral tumours and are not classified by stage or extent, nor is the extent of disease recorded for non-solid tumours like lymphoma and leukaemia. Treatment is notified with information on received or planned surgery, chemotherapy, radiotherapy, or endocrine therapy, or a combination of these modalities. More details, such as type of chemotherapy or target field or dose of radiotherapy are not registered.

## **Medical Birth Registry of Norway (MBRN)**

The MBRN was established in 1967, and is part of the Norwegian Institute of Public Health. Mandatory reporting from doctors or midwives attending the delivery and through antenatal health care visits ensures that all pregnancies in the country with a duration of at least 16 weeks (since 2002, from 12 weeks) are registered. The MBRN collects data on maternal health before and during pregnancy and demographic data about the parents, based on standardised notification forms from the antenatal health care visits and the maternity ward. Gestational duration, complications during pregnancy and delivery, pregnancy outcome including date of birth, anthropometric measurements, and vital status of the newborn, and eventual diagnoses made during the initial stay on the maternity ward are all notified. Initiation of pregnancy by ART has been registered since 1988, as IVF, ICSI, or technique not notified. Unsuccessful attempts to conceive using ART and adoptions are not registered.

Induced abortions are registered in The Register of Pregnancy Termination (a separate registry), which was established in 2006. Induced abortions are legal during the first 12 gestational weeks in Norway. From the 13<sup>th</sup> gestational week, a medical committee has to decide whether an abortion could be performed or not, upon application from the pregnant woman. In the MBRN database, only the late-induced abortions are included, usually based on ultrasound-detected foetal defects, and spontaneous abortions are only occasionally registered, depending on the duration of the pregnancy.

Gestational age is based on the date of the last menstruation, and since 1999, also on ultrasonographic estimations of gestation. Vital status of the newborn is registered as stillborn, alive at birth, death during the perinatal period (the first seven days of life), or death during the first three years of life. Immediate post-natal status is also given using Apgar score at one and five minutes, which has been registered since 1977. Delivery is notified as spontaneous or induced, and the use of caesarean section is listed, usually with additional information stating whether this operation was done electively or as emergency surgery.

## **Statistics Norway (SSB)**

SSB compiles individual-level information on all citizens in Norway. The institution was originally established as the Central Bureau of Statistics in 1876. For the present thesis, vital

status and educational status was provided by SSB. Educational status was used as a proxy variable of socioeconomic status in the analyses, given as education level at the time of inclusion. Educational level was categorised according to the total duration of education as low ( $\leq 9$  years), medium (10–14 years), high ( $\geq 15$  years), or unknown.

### **The Cause of Death Registry**

Underlying cause of death is registered, according to the International Classification of Diseases (ICD), since all deaths are reported by doctors who are required to complete a death certificate. The Section for Health Statistics at Statistics Norway is the Data Processor for the Cause of Death Registry, while the Norwegian Institute of Public Health is the Data Controller. Updated information about the date of death is provided to the CRN once a month, and cause(s) of death are provided once a year.

### **The Norwegian Population Register**

The control population for paper I and II was provided by the Norwegian Population Register. The register keeps demographic information on all citizens of Norway, including date of birth, date of death or emigration, and other personal information like marital status, children's date of birth etc. For this project, permission was granted by the Norwegian Population Register to draw cancer-free controls. The MBRN has access to the database of the Population Register, and established the control population. The data controller for the Norwegian Population Register is the Norwegian Tax Administration.

### **Approvals**

With permission from the National Data Inspectorate, the Regional Committee for Medical Research Ethics, and the registries/data controllers, data from the Cancer Registry were merged with data from the other data providers described above. No identifying information was provided to the researchers.

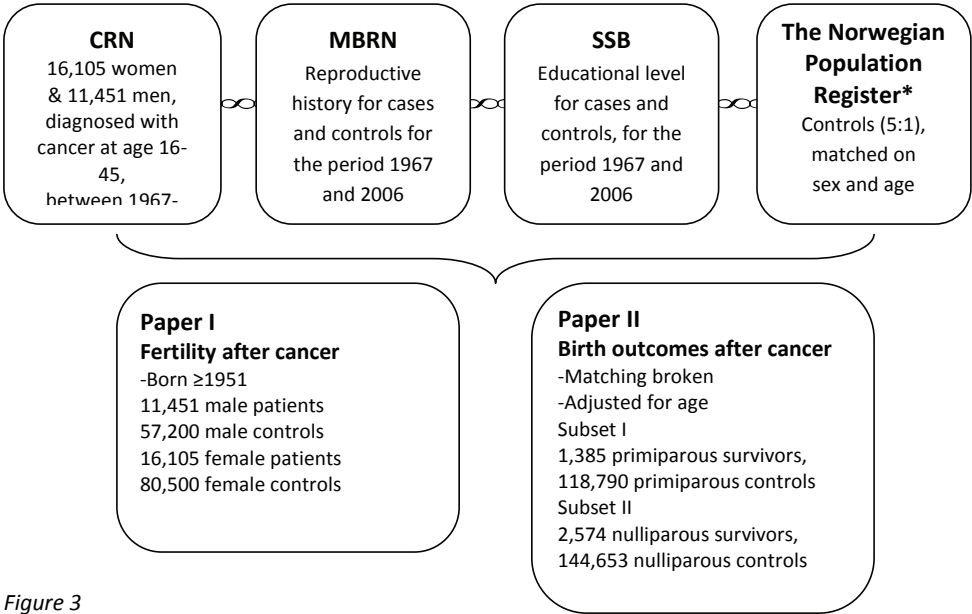
### **Data linkage and file construction**

For all papers, all malignant neoplasms according to the ICD-7 (140–207) were included, except basal cell carcinomas. In the case of multiple cancers in one person, only the first registered invasive malignancy was used in the analyses. Other eligibility criteria

compressed a histological confirmation and diagnosis prior to emigration or death, thus excluding cases diagnosed by autopsy. All cancer types combined were analysed, followed by separate analyses of the most frequent cancer types for the age group included. The most frequent cancer types were testicular, cervical, ovarian, breast, and thyroid cancer, malignant melanoma, brain tumours, Hodgkin’s and non-Hodgkin lymphoma, and leukaemia. Expressions like pregnancy and pregnancy outcomes are used similarly for both genders in papers I and II. In the following, each paper will be described regarding materials and methods, for further details see each of the papers. An overview is listed in *Table 3* at the end of this chapter.

**Paper I: Pregnancy after adolescent and adult cancer: a population-based matched cohort study**

Data from the CRN and the MBRN were merged, according to *Figure 3*, giving a total of 27,556 cancer survivors. To obtain the complete reproductive history for each person, we restricted our study to cancer patients who were 16 years or younger in 1967, when the MBRN was established.



*Figure 3*  
 Flowchart displaying the register linkage and study populations for paper I and II.  
 \*The MBRN constructed the control population file after permission from the National Population Register.



The main outcome was fertility after cancer, measured as the first post-cancer pregnancy. All registered pregnancies, regardless of duration and outcome, but with the date of last menstruation subsequent to the date of diagnosis, was included. An assigned “date of diagnosis” was defined for the controls, using the date of diagnosis for the matched survivor. For simplicity, the expression “post-cancer pregnancy” was used both for male and female cancer survivors and controls. We included only stage I patients with cervical and ovarian cancer (except for germ cell ovarian cancer), because the treatment of stage II–IV patients usually results in infertility. Borderline ovarian tumours were excluded. Sub-analyses of ovarian cancer were stratified according to epithelial stage I and germ cell or sex-cord tumours, because of prognostic and therapeutic differences.

Because cancer treatment information at an individual level is scarce in the CRN, we made an overview of general Norwegian treatment guidelines throughout the study period for the cancer types of interest. Stratification of the different treatment-related periods and interpretations were based on this table (see Table 1 in Paper I).<sup>160</sup>

## **Paper II: Birth outcomes among offspring of adult cancer survivors: a population-based study**

From the cohort of cancer survivors from paper I, all female and male survivors with at least one singleton pregnancy registered after cancer in the period 1967 to 2006 were selected (n=5,085). For the controls, the matching was broken and only those with at least one pregnancy registered in the study period, were used (n = 146,728, see *Figure 3* for more detail).

The main dependent parameters were pregnancy outcomes after cancer, which were analysed in two different parity subgroups for each gender. Nulliparous (first pregnancy ever after cancer) and primiparous (one pregnancy before and one after cancer) survivors were analysed. For comparison, we used all controls with at least one and two pregnancies, respectively.

The main pregnancy outcomes analysed were perinatal death, low birth weight (LBW, <2500g), preterm and very preterm birth (born <37 and <32 gestational weeks, respectively), low Apgar score<sup>161</sup> at five minutes (below 7), and congenital anomalies

according to EUROCAT.<sup>162</sup> We also evaluated mean birth weight, the use of IVF/ICSI, the occurrence of pre-eclampsia, and delivery by caesarean section.

Pregnancies shorter than 22 weeks of gestation, or with infants less than 500 g, were defined as spontaneous abortions (in accordance to WHO) and excluded. Consequently, perinatal death was defined as stillbirths with a gestational age of 22 weeks or more and weighing more than 500 g, death during delivery, or death during the first seven days of life. For analyses of preterm birth, misclassifications of gestational age were removed on the basis of current birth weight-by-gestational age standards, excluding z-scores larger than 4.<sup>163</sup>

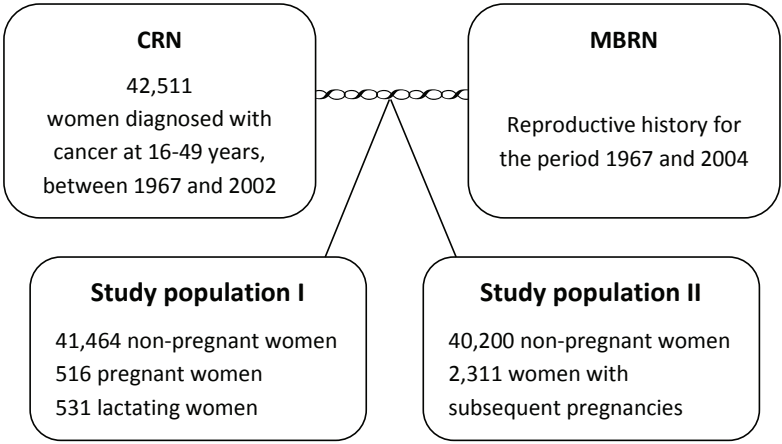
Congenital anomalies defined by EUROCAT excludes singular minor anomalies, those anomalies which are not truly congenital in origin (e.g. associated with immaturity at birth), and conditions poorly specified or often detected at a later stage of the infant's life. Examples of minor anomalies which are excluded, if they are isolated, are syndactyly, short fingers, haemangioma, pigmented nevus, torticollis, epicanthic folds, hiatus hernia, Meckel's diverticulum, and accessory or absent rib<sup>162</sup>. Congenital hip dislocations were also excluded from our analyses, as they might be detected at a later stage than the hospital examination.

### **Paper III: Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study**

Merging of registry data was performed according to *Figure 4*. Pregnant at diagnosis was defined as being diagnosed with cancer within the same month as their last menstruation until the date of delivery. Lactation period was defined as from the date of delivery to six months postpartum. If they experienced perinatal loss, the lactation period was defined as until two months postpartum. The women were not necessary lactating, but we wanted to focus on the post-natal period and the associated hormonal and breast tissue changes.

Females with subsequent pregnancies were defined as those having a pregnancy with last menstruation dated after the date of diagnosis. The comparison groups for analyses were females diagnosed with cancer, but without pregnancies associated with cancer diagnosis or after cancer, for simplicity, these were called non-pregnant. We analysed all sites combined and the most frequent cancer types for this age group.

The main outcome was cause-specific survival, defined as death by the same cancer type as that initially diagnosed, and with a date of diagnosis before the date of death.



*Figure 4*  
*Flowchart displaying registry linkage and study population for paper III.*

## Covariates

### Calendar year

We have studied a time period of almost 40 years, from 1967. During this period, several new cancer treatments have changed the prognosis dramatically, for instance the introduction of cisplatin. For pregnant women, the follow-up has changed as well during this period, most essentially with ultrasound examinations, but also with welfare improvements like longer periods of maternity leave. For paper I, diagnostic periods were established according to the treatment changes for the period 1967-2004, listed in Table 1 in the paper. For paper II, birth periods were used, instead of diagnostic periods, from 1967-1975, and further in 5-year intervals. For the third paper, the following diagnostic periods were used: 1967-1984, 1985-1994, and 1995-2002, based on timing of the main therapeutic changes during the period.

### Age

Age at diagnosis might influence the prognosis for certain cancer types. Furthermore, maternal age is linked to risk patterns for several pregnancy complications and birth outcomes. For paper I, the survivors and controls were age-matched on the time of the

survivor's diagnosis, so there was no need to adjust for age in the model. In paper II, the matching was broken, and we adjusted for maternal age (age at birth) in 5-year intervals (16-20, 20-24, 25-29, 30-34, and 35-45 years). In paper III, we used age at diagnosis, grouped into 5-year intervals, except for the first age group, 16-24.

### **Extent of the disease**

In all papers, we adjusted for the extent of disease in terms of localised, regional, distant and unknown. Exceptions from this categorisation are cervical and breast cancer, brain tumours, and haematological malignancies, as previously described.

### **Parity**

We adjusted for parity in paper I, categorised as childless, one child, and two or more children at the time of cancer diagnosis. In paper II, we stratified on parity by analysing nulliparous and primiparous individuals separately. For the cancer survivors, nulliparous meant the first pregnancy after cancer, and primiparous was used to mean having one pregnancy before cancer, and at least one after, where the second was focused on. The expressions nulli- and primiparous are used for both gender. The risks for stillbirth, LBW and preterm birth are higher for the first pregnancy than the second, and the risk pattern is not a linear function for, say the first three pregnancies.<sup>56</sup>

### **Educational level**

We used adjustments for educational level as a proxy for socioeconomic status. In papers I and II, we adjusted for educational level at the time of diagnosis for the survivors and at inclusion for the comparison cohort. Categorisation based on the number of years of education gave four levels: low (1-9 years, elementary and secondary school), medium (10-12 years, high school), high (13 years or more, college and/or university), or unknown. The proportion of unknown was 3% for survivors and 8% for controls in paper I, and 17% for survivors and 35% for controls in paper II. Educational level is not properly registered for immigrants, and is also underreported for the earliest birth cohorts.

## Statistical analyses

For all papers, standard descriptive methods were applied, using SPSS, with median and range or mean and standard deviation for continuous data and counts and proportions for categorical data. All tests were two-sided and  $p$ -values  $<0.05$  were considered statistically significant, except for paper III, where  $p$ -values  $<0.01$  were chosen. Hazard rates (HRs) or odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated for both crude and adjusted analyses.

### **Fertility after cancer (paper I)**

We used the Cox model or proportional hazards regression to compute post-cancer pregnancy rates for cancer survivors compared with those of the controls. The model was developed by D.R. Cox in 1972, and assumes that the ratio of the hazards comparing different exposure groups remains constant over time. The proportional hazards assumptions were checked by visual inspection of log–log plots. We performed separate analyses for each gender, for all cancer types seen together, and for selected diagnoses. We stratified by matched sets, consisting of a survivor and his/her five corresponding controls. The observation time was defined as the interval from the actual or the assigned date of diagnosis to the date of the first birth after cancer. Censoring was made for death, emigration, or when the person reached the age of 46, or December 31, 2006, whichever occurred first.

Cumulative hazards distributions display how the hazards vary if an event varies with time. Since the prognosis is quite poor for several of the cancer types included, death as a competing event to initiating a pregnancy after cancer was thus incorporated into the analysis, and was depicted as cumulative incidence. The competing risk approach is used as a supplement to the proportional hazards model, which involves treating the competing events by censoring.

### **Birth outcomes (paper II)**

Descriptive analyses with Chi-square and multiple logistic regression models were used to compare birth outcomes for survivors and controls. Multiple logistic regressions predict the probability of an event, and take into account several explanatory factors (confounders). The

estimate is given as an odds ratio. The model compares the odds of, for example, LBW for the offspring of cancer survivors (the exposed ones) to the odds of LBW for the offspring of the controls (not exposed). Further, we used a univariate ANOVA model to assess mean birth weight, both crude and adjusted for maternal age. The same model was repeated to assess mean birth weight in a cohort excluding malignant melanoma patients, as previously described, to simulate the selection used in the hospital-based study by Magelssen *et al.*<sup>2</sup>

### **Cause-specific survival (paper III)**

Using the Cox model, two different subsets were analysed with cause-specific survival as the outcome. The first subset explored survival if the cancer was diagnosed during pregnancy or lactation, and the second investigated survival in cancer survivors with at least one subsequent pregnancy. We used analyses of Schoenfeld residuals in order to test the proportional hazard assumption. Multivariable analyses were conducted to assess potential confounding by the covariates listed above.

For the second analysis, we introduced a time-dependent variable. All survivors started out as non-pregnant (reference group), and the women who had any pregnancy starting after the date of diagnosis were moved into the post-cancer pregnancy group at the date of delivery. The women who finally constituted the post-cancer pregnancy group contributed time at risk in the reference group until the date of the first delivery after cancer, from which date the follow-up started.

With death as the outcome event in both analyses, end of follow-up was defined as reaching age 60, emigration, or 31 December, 2004, which led to censoring. Trends in proportional changes per year of incidence of cancer diagnosed during pregnancy or lactation were tested by a log-linear model with calendar year as a continuous variable.

Table 3

Overview over the three papers included in the thesis, regarding material and methods.

| Papers included                       | Paper I – fertility after cancer   | Paper II – birth outcomes   | Paper III – cause-specific survival  |
|---------------------------------------|--|---|--|
| <b>Title</b>                          | Pregnancy after adolescent and adult cancer: a population-based matched cohort study   | Birth outcomes among offspring of adult cancer survivors: A population-based study  | Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study   |
| <b>Main purpose</b>                   | Compare incidence of pregnancies after cancer with the number of pregnancies in a cancer-free, age-matched controls group, analysed separately for females and males   | Compare birth outcomes among the offspring of the cancer cohort and the cancer-free cohort. Analysed separately for females and males and by parity<br>i) in nulliparous<br>ii) in primiparous                  | Compare survival in<br>i) females with cancer during pregnancy or lactation with non-pregnant females with cancer<br>ii) females with subsequent pregnancies with females without pregnancies after cancer |
| <b>Study design</b>                   | Population-based historical cohort   | Population-based historical cohort  | Population-based historical cohort of female cancer patients   |
| <b>Study population; definition</b>   | Survivors: Females and males, diagnosed in the period 1967-2004 at age 16-45 years<br>Controls: Five per survivor, matched on age and gender. The controls were given an assigned date of diagnosis  | Survivors: Females and males, diagnosed 1967-2004 at age 16-45 years and with a subsequent pregnancy (1967-2006)<br>Controls: All from paper I with at least one pregnancy in the period 1967-2006              | Females diagnosed with cancer in the period 1967-2002, at age 16-49 years old.   |
| <b>Follow-up periods</b>              | Cancer: 1967-2004<br>Pregnancies: 1967-2006  | Cancer 1967-2004<br>Pregnancy outcome: 1967-2006  | Cancer: 1967-2002<br>Death/pregnancies: 1967-2004  |
| <b>Observation period; definition</b> | From the actual or assigned date of diagnosis to the date of the first birth after cancer, death, emigration, age of 46, or December 31, 2006, whichever occurred first  | Not relevant  | From the date of diagnosis until date of death, emigration, age of 60, or until December 31, 2004, whichever occurred first  |
| <b>Statistical approach</b>           | Cox model, competing risk (cumulative incidence)   | Logistic regression   | Regular Cox model and time-dependent Cox model   |
| <b>Adjustments</b>                    | -Diagnostic periods: according to treatment periods (Table 1, paper I)<br>-Pre-diagnostic parity: 0, 1, 2+<br>-Extent of disease*: Localised, regional, distant, and unknown.<br>-Educational level: Low ( $\leq 9$ yrs), medium (10-14 yrs), high ( $\geq 15$ yrs), unknown | -Birth periods: 1967-1975, further in 5-year intervals<br>-Maternal age: <20 years, 20-24, 25-29, 30-34, 35+<br>-Educational level: Low ( $\leq 9$ yrs), medium (10-14 yrs), high ( $\geq 15$ yrs), and unknown | -Diagnostic periods: 1967-1984, 1985-1994, 1995-2002<br>-Age at diagnosis: $\leq 24$ , 25-29, 30-34, 35-39, 40-44, 45-49<br>-Extent of disease: Localized, regional, distant, and unknown.                 |

*\*For gynaecological cancer, FIGO stage I-IV, breast cancer stage I-IV (localised, regional lymph node metastases, direct tumour extension to the chest wall or skin, or distant metastases). Brain tumours and non-solid tumours are not classified by stage or extent. See table 1 in paper I for the selected stages included in the analyses.*

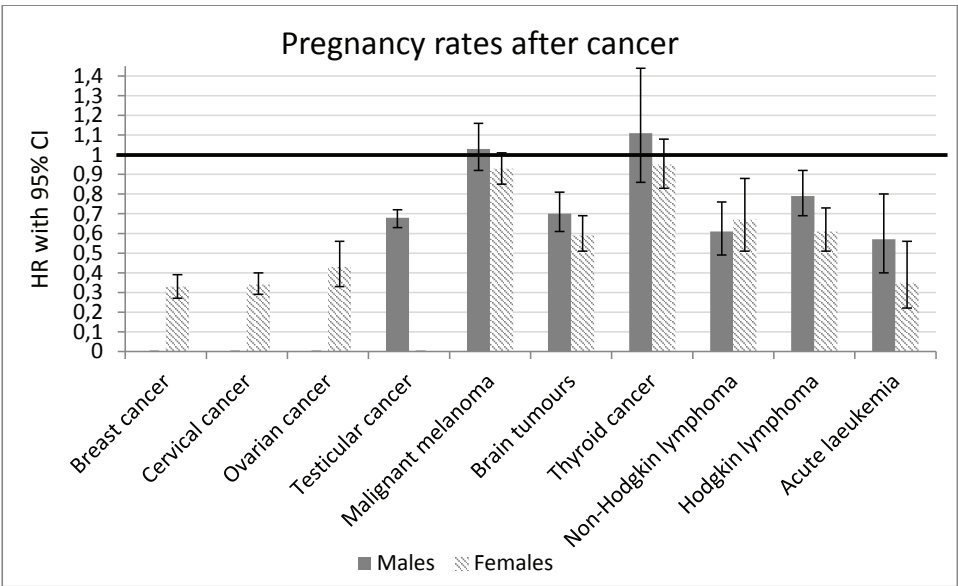




# SUMMARY OF RESULTS

## Fertility after cancer (Paper I)

Cancer survivors had, in general, lower pregnancy rates than controls, but the rate was higher in males than in females (HR = 0.74 [95% CI 0.71–0.78] and HR = 0.61 [95% CI 0.58–0.64], respectively). However, both male and female survivors of malignant melanoma and thyroid cancer did not differ from their controls. The other malignancies with high pregnancy rates after cancer were testicular cancer, Hodgkin lymphoma among males, and non-Hodgkin lymphoma among females. In contrast, the lowest hazard rates for pregnancy occurred in female survivors of leukaemia, breast, or cervical cancer stage I (*Figure 5*).



*Figure 5*  
*Pregnancy rates after cancer for both female and male cancer survivors. The columns represent HR, and the error bars 95% CI.*

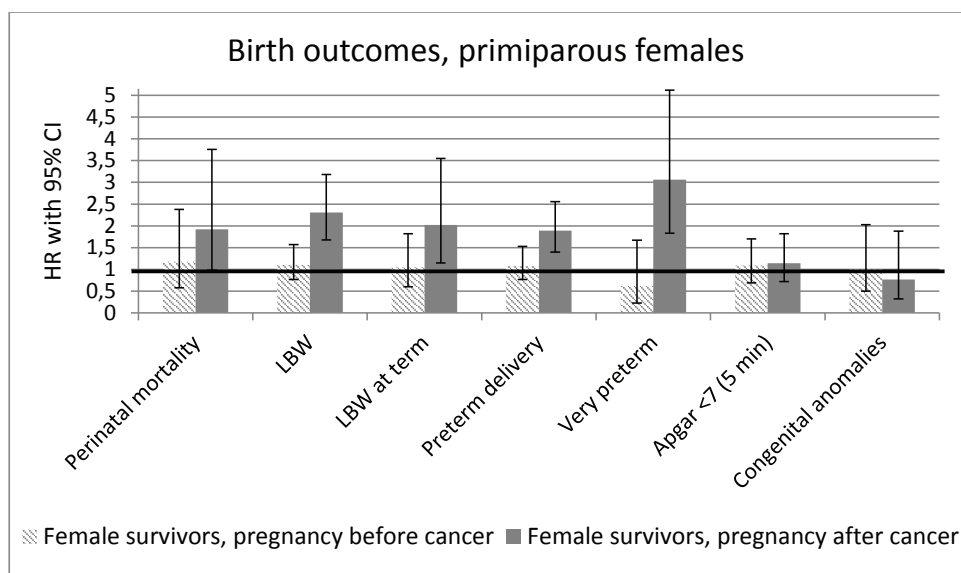
The pregnancy rates increased during the study period for all ovarian cancer types of stage I (HR = 0.19 [95% CI 0.11–0.32] to HR = 0.67 [95% CI 0.49–0.90]), testicular cancer (HR = 0.61 [95% CI 0.43–0.86] to HR = 0.76 [95% CI 0.70–0.83]), and for men diagnosed with HL (HR = 0.68 [95% CI 0.53–0.87] to HR = 0.87 [95% CI 0.73–1.04]). When taking parity into account, female survivors had lower pregnancy rates if they had at least one child at diagnosis compared to those childless at diagnosis (HR = 0.52 [95% CI 0.48–0.56] versus

HR = 0.73 [95% CI 0.67–0.78]), while for male survivors, parity did not have any difference in the rate of initiating a pregnancy after cancer. Successful assisted reproductive technologies (ART) were used by 6% of male cancer survivors to initiate a pregnancy after cancer, while only 2% among the controls became pregnant by ART ( $p<0.001$ ). For females, the use of ART was similar for survivors and controls (2% for both groups). Competing-risk plots were made to determine whether there was a catch-up effect during the 15 years of observation after diagnosis, but no real catch-up effect was observed for the cancer survivors compared to the controls for any of the malignancies analysed.

### **Birth outcomes (Paper II)**

The infants born to nulliparous female survivors (having their first pregnancy after cancer) had an increased risk of preterm delivery (HR = 1.30 [95% CI 1.05–1.61]) and LBW (HR = 1.26 [95% CI 0.99–1.60]). Nevertheless, when restricting the analyses of LBW to term infants, the increased risk of cancer survivors' offspring disappeared. In comparison, for primiparous female survivors, the outcome of the second pregnancy differed from the controls, with a higher risk of LBW and preterm birth. Even when restricted to infants born at term, the risk of LBW was still doubled. A borderline significant increase of perinatal death was seen for primiparous female survivors, with OR=1.92 (95% CI 0.98–3.76, *Figure 6*).

There was no increased risk of congenital anomalies for the offspring when analysing all cancer types combined for each gender and parity group separately, not even when restricted to analyses of females giving birth within two years. When analysing the most frequent cancer types separately, the only increased risks of malformations were found in offspring of primiparous breast cancer survivors (OR=3.49 [95% CI 1.24–9.82]), and in offspring of nulliparous ovarian cancer survivors (OR=3.23 [95% CI 1.54–7.23]). The different anomalies are displayed in *Table 5*. In breast cancer survivors who were only initially treated by surgery, the risk estimate was still elevated, but not significantly (OR=1.65 [95% CI 0.22–12.30], not tabulated).



**Figure 6**

*Effects on birth outcomes to primiparous female cancer survivors compared to their controls with similar parity. HRs with 95% CIs for the outcomes of the first birth, the one before cancer diagnosis, is depicted for comparison.*

ART was used more frequently among male survivors than controls to achieve a pregnancy after cancer, both among nulliparous (HR = 1.83 [1.35–2.49]) and primiparous (HR = 4.01 [95% CI 2.53–6.35]) survivors. Surprisingly, ART was also frequently used among primiparous females to initiate the pregnancy before cancer (HR = 2.85 [95% CI 1.46–5.56]), but they did not differ from their controls regarding the use of ART for the pregnancies after cancer.

Primiparous female survivors had doubled the risk of giving birth by caesarean section (HR = 1.75 [95% CI 1.43–2.15]), and pre-eclampsia also occurred more frequently among primiparous female survivors compared to their controls, (HR = 1.58 [95% CI 1.04–2.39]). For a subgroup of primiparous females where the malignant melanoma survivors were excluded (to compare with the cohort and results in the study by Magelssen *et al.*<sup>2</sup>), a significant difference in mean birth weight was demonstrated for the second sibling, with lower birth weight for the survivors' than controls' offspring (depicted in figure 2 in paper II). Otherwise, mean birth weight was similar for offspring of survivors and controls.

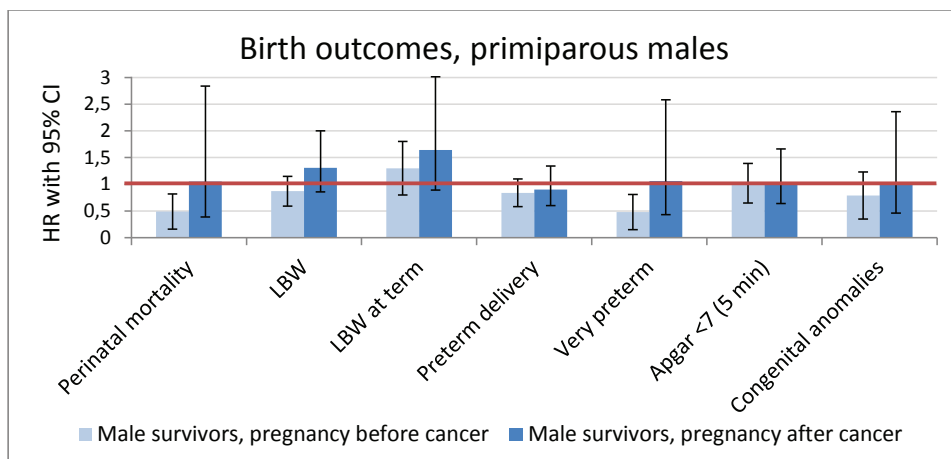


Figure 7

Effects on birth outcomes to primiparous male cancer survivors compared to their controls with similar parity, depicted as HRs with 95% CIs for the first and second birth.

### Cause-specific survival (Paper III)

Our results revealed that, in Norway, about 1 in 2000 pregnancies is associated with cancer, diagnosed during pregnancy or the lactation period (first six months post-partum). The incidence of cancer associated with pregnancy increased during the study period (*Figure 8*).

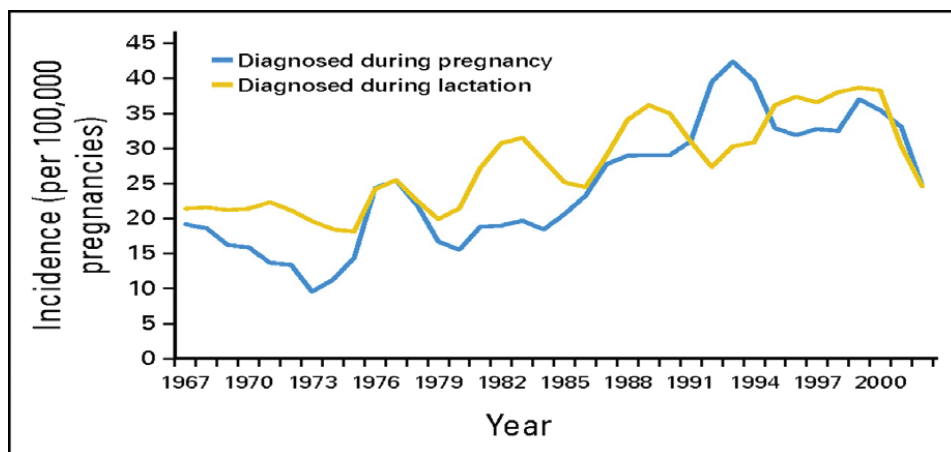
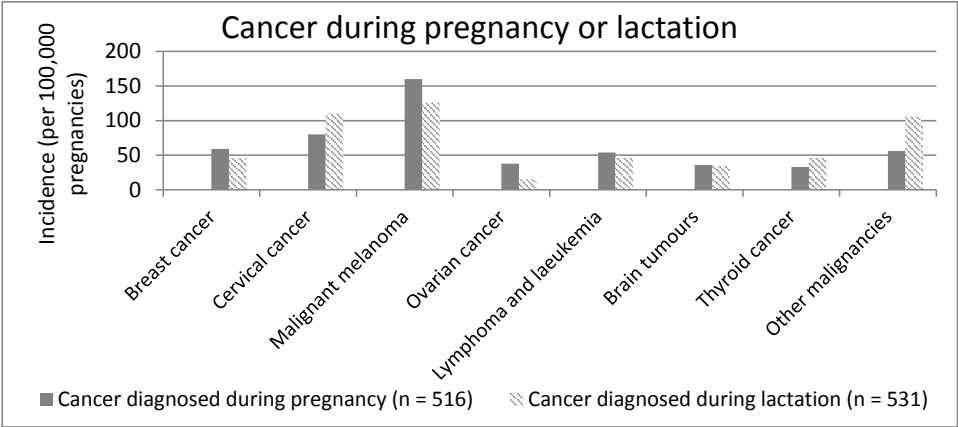


Figure 8

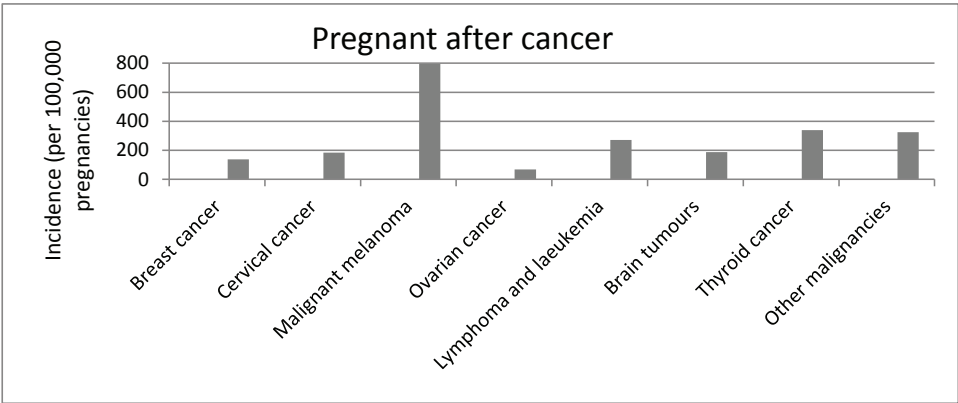
Annual incidence of cancer diagnosed during pregnancy or lactation, using 3-year moving averages, shown as proportions per year per 100,000 pregnancies. Annual incidence of cancer diagnosed during pregnancy or lactation, using 3-year moving averages, shown as proportions per year per 100,000 pregnancies. Reprinted with permission. ©2009 American Society of Clinical Oncology. All rights reserved. Stensheim et al. JCO 2009;27:45-51.<sup>164</sup>

The mean annual incidence of cancer during pregnancy in the period was 24.5 per 100,000 pregnancies and for cancer during the lactation period 27.7 per 100,000 pregnancies. The annual increase during the period was 2.5% (95% CI 1.7–3.3) and 1.6% (95% CI 1.0–2.4), respectively, for cancer diagnosed during pregnancy and lactation.

The most frequent cancer types during pregnancy or lactation were found to be malignant melanoma, cervical cancer, and breast cancer, in that order (Figure 9). The survivors of malignant melanoma, thyroid cancer, and lymphoma and leukaemia most frequently become pregnant after cancer (Figure 10).

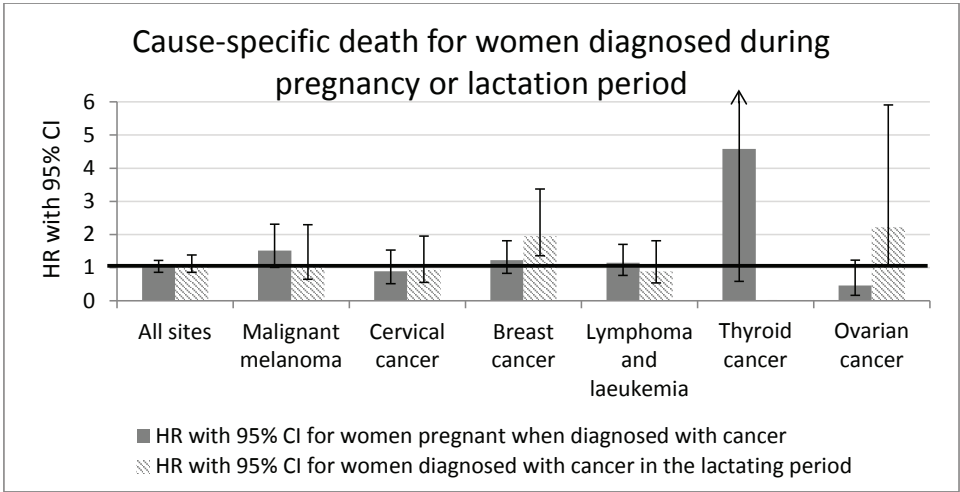


**Figure 9**  
The order of the cancer types on the x-axis is reflecting the frequency of the different cancer types for all females who were diagnosed in the age group 16-49 years. The columns depict the numbers diagnosed with the different cancer types during pregnancy or lactation.



**Figure 10**  
The most frequent cancer types diagnosed in females with subsequent pregnancies, n = 2,311.

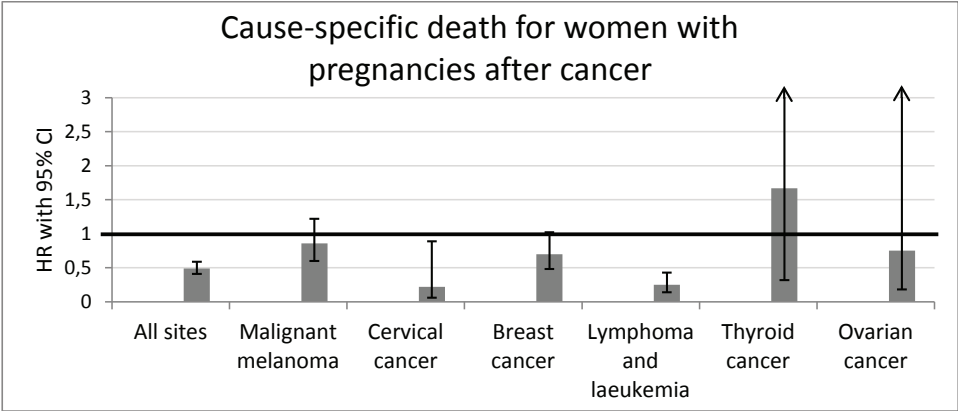
For all sites combined, no differences in cause-specific death were seen for the pregnant and lactating groups compared to their controls. Patients with breast (HR, 1.95 [95% CI 1.36-2.78]) and ovarian cancer (HR, 2.23 [95% CI 1.05-4.73]) diagnosed during lactation had an increased risk of cause-specific death.



**Figure 11**  
Hazard rates for survival of women diagnosed with cancer during pregnancy or during the lactation period. The upper CI limit for thyroid cancer diagnosed during pregnancy was 35.9. No one diagnosed with thyroid cancer died in the lactation period group.

Diagnosis of malignant melanoma during pregnancy also increased the cause-specific risk of death (HR=1.52 [95% CI 1.01-1.22]), but if localisation of the melanoma was adjusted for, the HRs were reduced to 1.45 (95% CI 0.96-2.21). We found a difference in the site distribution of melanomas between those diagnosed during pregnancy and those who were not pregnant, with a higher frequency of head, neck, and trunk melanomas among the pregnant group, while the non-pregnant individuals had a higher frequency of leg melanomas. In an additional analysis, we adjusted for tumour depth according to Breslow, when available (55% of the patients), but did not find any difference in survival compared to the controls. Finally, we combined the groups diagnosed with malignant melanoma during pregnancy and during lactation, and did not find a worse survival in comparison with the non-pregnant population: HR=1.33 (95% CI 0.95-1.86).

For all sites combined, the risk of cause-specific death was significantly decreased for women who had subsequent pregnancies (HR=0.49; 95% CI 0.41-0.59), and similar findings were seen for cervical cancer and leukaemia and lymphoma with subsequent pregnancies, while the other cancer types analysed separately did not differ from the cancer survivors, with no post-cancer pregnancies (see *Figure 12*).



*Figure 12*  
HR with 95% CI for women pregnant after cancer, compared with women with no pregnancies after cancer. The upper CI limits for thyroid and ovarian cancer were 8.8 and 3.0, respectively.





# DISCUSSION

## Methodological considerations

### Design

This thesis includes three observational cohort studies. A cohort is a defined group of individuals who are followed from a given time point or inclusion event, over a period of time, in order to explore whether there are causal relationships between the occurrence of a disease (or another event) and future outcome. It is the archetype for all epidemiologic studies, in contrast to case-controls studies, which are classified as the second most convenient design for epidemiologic studies. A case-control study is based on a sample from a source population. Incidence rates or risks can be calculated from a cohort design, which is well-fitted to study many types of outcomes.<sup>165;166</sup>

Observational studies can be retrospective in the sense that data have already been collected, but prospective in the meaning of following individuals from, in our case, cancer diagnosis until a future event takes place. Both cohort and case-control designs offer high precision. The accuracy of observational epidemiologic studies might be influenced by two types of errors, systematic and random errors. Systematic errors result from selection bias, information bias, and confounding, whereas random errors are related to statistical precision. This will be further discussed in the following sections.

For paper I, all cases with cancer diagnosed in the age group 16-45 years were followed from a cohort of the entire Norwegian population of all males and females born in 1951 or later. For every male and female with cancer, five age- and gender-matched controls were randomly selected from the Norwegian Population Register to assess the pregnancy rates after cancer, and for the controls after the assigned date of diagnosis. It can be thought of as a cohort study, with a survivor cohort (exposed to cancer) compared to a sample of the entire cancer-free cohort. Another useful design would have been a typical cohort design, where the comparison group was made up of the whole cancer-free population in Norway for the chosen age group and period. Further, we could have started follow-up at the time of birth, and not from the time of cancer diagnosis, in order to determine to what degree cancer survivors had a first birth compared to the general population, as done by Syse *et al.*<sup>24</sup>

Collecting a random sample from the cohort of cancer-free persons offers less statistical precision than using the full cohort, but similar estimates are expected to be achieved by using five or more controls per case, compared to using the whole population as controls.<sup>166</sup> In these preparations, we also used a model where matching was ignored and age was adjusted for as a covariate. This gave similar results to the matched model.

In paper II, a cohort of all males and females diagnosed with cancer and with registered pregnancies after cancer was selected from the material in paper I. They were followed to assess whether the offspring had adverse birth outcomes or not, compared to a sample from the general population. The matching from the original material (see paper I) was dissolved to make estimation of birth outcome possible with adjustment for maternal age. The initial file was matched on the day of birth. This design can also be looked upon as a case-control study nested within a cohort (of all Norwegians with at least one pregnancy). The mean age differed slightly among the survivor and control groups, and the number of patients for each birth period differed as the control cohort was larger for the first period. To take care of this imbalance, we used multivariable statistical analyses with adjustments for age and birth calendar period. To avoid this step of breaking the originally matched design and the possible insecurity introduced, a preferable design would have been to use all cancer-free individuals registered in the MBRN in the chosen period as controls (as done by Magelssen *et al.*<sup>2</sup>).

Since Magelssen *et al.*<sup>2</sup> had published a mono-institutional study about birth outcome after cancer based on material from the Norwegian Radium Hospital (NRH) in 2007, we wanted to make close comparisons. Therefore, we excluded malignant melanoma survivors from sub-analyses on birth weight and the main pregnancy outcomes for the offspring to compare estimates. More than 30% of the females and about 20% of the males in our material were diagnosed with malignant melanoma, while the corresponding figures in Magelssen's material based on patients at the NRH were quite small: 5% and 1%, respectively.<sup>2</sup> The majority of those reported to the CRN with malignant melanoma for this age group likely had stage I disease, with no need for systemic treatment.

In paper III, a historical cohort design was applied, using all females with a cancer diagnosis in the age group 16-49 years. They were followed to assess survival, comparing

groups related to the time of pregnancy (pregnant at diagnosis, lactation period when diagnosed, or with a subsequent pregnancy, compared to those who were nulliparous or experienced all their pregnancies before the time of cancer diagnosis).

## **Survival analyses**

We have performed survival analyses in two papers. It can also be applied to non-fatal risks as future events following an exposure, like getting pregnant or not, after a diagnosis of cancer.

Survival might be defined as observed or relative. Observed or overall survival is a measure of the proportion of individuals who survived for a specified time period without addressing the cause of death, often starting at the time of cancer diagnosis. For example, we often give prognostic information about cancer in five-year survival, which is based on the proportion being alive five years after diagnosis. Relative survival relates observed survival to that expected in a group from the general population with similar age and gender, which is known as net survival. In paper I, we used the Cox model to investigate pregnancy-rates after cancer. We analysed cause-specific survival in paper III, which is sometimes called corrected survival. Cause-specific survival is a net survival measure representing cancer survival in the absence of other causes of death. Cause-specific survival is corrected by censoring those who died of causes other than cancer. We have used the expression cause-specific survival. Since the risk estimates are representing a risk of death, we could instead have called it cause-specific mortality.

As cause of death, we have used the underlying cause of death. Since the correct diagnosis might be difficult to determine sometimes, especially in elderly people, we restricted the follow-up time to age 60. Autopsies are seldom performed in Norway nowadays (less than 10% of all deaths), but more often in younger persons. The cancer diagnosis is usually the underlying cause of death if a person still had symptoms of his or her malignancy. A recent paper revealed that cancer as the underlying cause of death had the highest accuracy compared with other diagnoses, when undertaking autopsy findings in addition to death certificate information. They also found a small underestimation of cancer as the cause of death.<sup>167</sup> It is a known limitation with cause-specific survival analyses that for some survivors, the malignancy might have contributed to the cause of death, but they are still

given a non-malignant diagnosis. There are also other reasons for the cause of death information being unreliable or unknown. For example, if a cancer has metastasised to another site, the death certificate may list cancer of the metastasised site as the cause of death. One possible way to address this problem is to only include individuals with one primary cancer and define the cause of death as all cancers. However, we listed only nearby sites as a real cause-specific death, and censored those who had a totally different cancer diagnosis as cause of death than the initial diagnosis listed in the CRN. We also assessed overall survival at age 60, which, in numbers, differed by 1-3% from the number classified with a cause-specific death.<sup>164</sup>

In paper I, we performed competing-risk-analyses in addition to Cox regression, since the risk of death for some cancer types and stages are competing with the probability of achieving a pregnancy after cancer, at least for women. Therefore, we performed competing risk plots to estimate the cumulative incidence of pregnancies after cancer, in comparison with controls. Estimates were also computed, and in comparison to the hazard rates obtained from Cox regression, we found very similar estimates. Death is treated as censoring in the Cox regression. At least for certain cancer types and periods, the risk of death was higher than the probability of having a pregnancy after cancer, for example for breast cancer, while malignant melanoma and thyroid cancer survivors showed equal probabilities to conceive after cancer as their controls, even if the risk of death was higher for the cancer survivors than for controls (*Figure 13*). We expected a small catch-up effect for some of the cancer types with early recurrence, but no such convincing effect was seen by inspecting the plot. Probably, there might be a minimal such effect seen for Hodgkin lymphoma among females in the period 1967-1987 (figure 2, paper I). This might reflect the competing risk and decreased fertility for the first years after cancer, as well as the general advice given to cancer patients, to delay pregnancy for at least two years after diagnosis.

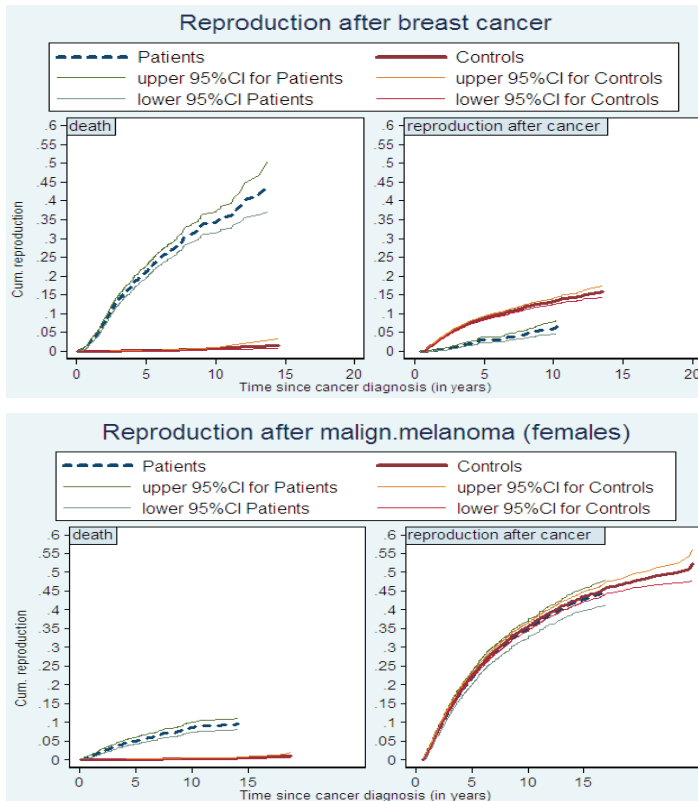


Figure 13

Competing risk plots. The x-axis shows time since cancer diagnosis and the y-axis measures cumulative risk of death versus probability of having a pregnancy after cancer.

The time-dependent Cox regression used in paper III is chosen to take care of two events, diagnosis of cancer, and the following event, a subsequent pregnancy. Kaplan-Meier or regular Cox model analyses are not suitable for such situations, since all females in the group who had a subsequent pregnancy stayed alive at least until the first birth. In contrast, females in the comparison group, they who did not have pregnancies after cancer, were at risk of dying from day one in the follow-up period. Studies have been performed without taking this into account.<sup>168</sup>

## Validity

Validity is divided into two components. Internal validity reflects whether the observed findings are representative for the entire groups studied. Internal validity is influenced by

selection bias, information bias, and statistic validity, which are explained below. The observations in this thesis are looked upon as valid and representative for the Norwegian population (internal validity). External validity reflects to what extent the findings could be applied to another population than the group studied, representativeness. External validity is influenced by study design which is influenced by random or systematic errors.

The comparison groups used in paper I and II might be theoretically healthier than the general population they are sampled from and meant to represent, as they are cancer-free at least until the time of diagnosis for the index case. Practically, this is negligible, also since the age group studied is younger than 46 years.

Our findings might be valid for other populations similar with ours, at least the Scandinavian populations, but cancer incidence patterns and treatment guideline factors linked to society, economy, educational level, and social welfare system will influence to what degree the external validity can be accounted for in all populations (external validity).

One might argue that parts of the cancer cohort studied represent outdated treatment. This might reduce the generalisability of our results to current cancer patients, both in our population and worldwide. Treatment and diagnostic procedures, age at first birth, and the mean number of children have changed during the study period. Still, the understanding of biological effects of previous cancer treatment might be of interest, like the finding of increased numbers of pregnancies registered among survivors of ovarian or testicular cancer, and among males diagnosed with HL.<sup>160</sup> The understanding of the diagnostics and treatment for the more historical proportion of the cohort is still of relevance, in the perspective of cancer survivorship research.

### **Selection bias**

Such bias results from the selection of participants for a study, where the relation of the exposure and the disease or event studied, is differently dispersed among those included and those not. For registry-based studies like ours, the observations are most likely prevented from selection bias. Mandatory registration of cancer and births prevent selection bias. The control population for study I could possibly have been influenced by selection bias if the individuals chosen were matched on more than age and gender, and for study II the controls

have a little different age distribution, the control of which is attempted through adjustments for maternal age and calendar period.

For simplicity, we excluded survivors of cervical and ovarian cancer stage II-IV in paper I, since the treatment usually requires hysterectomy and thereby makes future pregnancies impossible. One might argue that treatments for other cancer types also imply a high risk of infertility. Since no detailed treatment information was available, however, we chose to adjust for stages of other cancer types, which did not necessarily impose infertility. If not fully adjusted, this selection of eligible individuals might give an estimate reflecting a heterogeneous group, for example for breast cancer survivors, since some of them might be infertile after treatment.

Another type of selection bias, which is present in paper III, is self-selection when it comes to having a child after cancer. This is called the “healthy mother effect” and influences all analyses comparing survival among cancer survivors with and without subsequent pregnancies.<sup>99</sup> The explanatory factors for the healthy mother effect are most likely better prognosis (low grade tumour) and less cancer treatment, eventually lower age at diagnosis than those not getting pregnant afterwards, and being in good health after cancer.

### **Information bias**

If there are errors in the measurements of variables regarding exposure and outcome, information bias is present, which can lead to false conclusions. In registry-based studies, the risk of information bias is substantially reduced, as recall bias is not a problem. Still, there might be information bias introduced by misclassifications and random errors, including typing errors and data processing errors. Being misclassified describes the situation where individuals are placed in the wrong category, for example if those with cancer *in situ* are categorised as having invasive cancer. Misclassifications could be of two types: differential misclassifications and non-differential. About 0.5-1% of typing errors must be accounted for in registry-based materials, but such errors are likely to be similarly spread among cases and controls, and are usually disregarded.

A differential misclassification occurs when the classification of outcome is dependent upon the status of the exposure, or vice versa. This is the situation when misclassification may

vary between groups (e.g. is differently dispersed among survivors and controls). For example, one might think that the detection and registration of congenital anomalies among offspring of cancer survivors could be made earlier than for the cancer-free population, since there is a reason for higher awareness in the first group. Since the registrations are made upon examinations in hospital during the first three to four days of life, this type of error should be minimised.

A non-differential misclassification occurs when the probability of misclassification is the same, regardless of the study group, for instance survivors and controls. Non-differential misclassification will introduce bias towards the null, leading to an underestimation of the associations. The registration of fathers in the MBRN is based on information from the mother. This might lead to a number of fathers that only are social, not biological fathers. It is likely that there are no differences among cancer survivors and the cancer-free population in this regard. There is also a general underestimation of the number of fathers, up to 2%, since not all fathers are reported to the MBRN.<sup>27</sup>

### **Potential misclassification of exposure variables**

Less than 3% of the cancer cohort used in this material is registered with more than one malignant diagnosis. The information about the second and eventual subsequent cancers is not used, and since recurrences are not registered, we have only focused on the first invasive diagnosis for all three studies.

Regarding the extent of disease or stage, registration has varied through the period studied. In cases lacking information, the code “unknown” should be used, but this parameter seems to have been used more frequently for some malignancies than others during several periods. Unfortunately, this results in more than 30% of cases having unknown extent during several calendar year periods, illustrated by breast cancer in paper I, for instance.

The registrations of miscarriage tend to be underreported for the beginning of the second trimester. Even if the reporting is mandatory from gestational week 12 (16 before 1999), late miscarriages (gestational week 12-21) usually lead to hospitalisation, but in the Gynaecologic department, not the Obstetric, and are attended by a doctor, not a midwife. For later years, the electronic medical record systems in the Gynaecologic departments are



not compatible with the report form to the MBRN, and require hand-written forms instead. From 2006, induced abortions were not reported to the regular MBRN, but to the separate Termination of Pregnancy Registry. Late terminations (gestational week  $\geq 12$ ) have been reported since 1999. The underreporting makes it impossible to explore whether spontaneous and induced abortions are more common among female cancer survivors than the general population, and for the recent years, whether congenital anomalies are detected in early pregnancy and have led to terminations to a higher degree among cancer survivors than controls. Similarly, the possible differences in registration make it necessary to define stillbirth as from gestational week 22.<sup>169</sup>

## **Confounding**

A confounder is a variable which is associated with both the outcome and the exposure, without being a consequence of the exposure. To be a confounding factor, it must have an effect and be imbalanced between the groups in order to be compared. Confounding factors either create a spurious association or mask a real association between the exposure and the outcome. To prevent confounding, randomisation, restriction, or matching are common procedures. Randomisation is only possible in experiments. Restriction means choosing subjects for the study who have the same or nearly the same value for a variable that might be a confounder (solved by analysing males and females separately, for instance). In epidemiologic studies, the common procedure for controlling for confounding adequately is to use stratification or adjustments.<sup>166</sup>

Calendar time, age, extent of disease, parity, and socioeconomic status were the known potential confounders accounted for in the analyses. In study I, we stratified by age, using randomly drawn controls matched by gender and date of birth, since age is closely related to the possibility of having a future pregnancy. For the study of pregnancy-associated cancer and cause-specific survival, educational level was not obtained, which could be looked upon as an unmeasured confounder. For the study about birth outcome (II), we adjusted both for maternal age (at birth) and for calendar period. There have been changes during the study period regarding several of the confounding factors. Increase in maternal age at first birth, introduction of ultrasound during pregnancy, changes in obstetrical practices, and attainment of higher educational level are all factors which influence the risk of adverse birth outcomes.

With our stratification on parity in paper II, it might be argued that comparison with other studies is more difficult. Most studies on birth outcomes after cancer have not stratified on parity, some compare all pregnancies after cancer, and others make adjustments for birth order.<sup>23;74-76</sup> Still, parity effects are seldom dealt with in studies exploring outcomes for offspring, but might strongly influence the results with dilution or overestimation effects of cancer on pregnancy outcome.

Unmeasured confounders included maternal smoking history. Smoking habits have been registered in the MBRN since 1999, if the woman gives her consent to such registration, unlike most other variables. It is reported that the proportion of daily smoking pregnant women at the end of pregnancy was 34% in the lowest level of education, 16% in the intermediate level and only 5% in the highest level of education for the period 1999-2004.<sup>170</sup> There has been substantial variation during the study period of the proportion of daily smoking pregnant women, and for recent years the number has declined further.<sup>27</sup>

### **Residual confounding**

Residual confounding remains after adjustments for all known confounding factors. With the imperfect categorisation of variables, like treatment or stage, given in very coarse terms, the outcome estimate might be influenced by residual confounding. An example is breast cancer diagnosed during the lactation period, in paper III, where HR declines from 3.44 to 1.95 going from uni- to multivariate analyses.

### **Precision and lack of random errors**

Even if the whole material is nationwide, sub-analyses have smaller numbers and few events. We have used 95% confidence intervals, meaning that there is a 5% possibility that the observed association is due to chance. The broadness of the interval reflects the precision.

If a study incorrectly rejects a null hypothesis, meaning that analyses show that a difference does exist when it does not, this is called a type I error. For instance, this might be the case in paper II, where sub-analyses for different cancer types with congenital anomalies as the outcome, resulted in significantly increased risk among offspring of primiparous breast and

nulliparous ovarian cancer survivors. The events were few: 4/43 and 4/44, respectively. Additionally, the increased risks were only found for one of the parity groups for each cancer type, not both.

If there is no apparent difference among the groups studied, indicated by a  $p\text{-value} > 0.05$ , despite the existence of a real difference, it is called a type II error. If a test is underpowered, the type II error is large, resulting in difficulty in detecting a real effect, if the effect indeed exists. This might for instance have been true for other cancer types with regard to congenital anomalies, where the number of events, and thus, the power of the test, was low.<sup>165</sup>

### **Advantages and limitations of registry-based materials**

We have conducted three population-based studies, including all cancer patients in Norway with an age of 16-45/49 at diagnosis over a period for more than 35 years. The registry-based data are virtually complete, because of mandatory reporting, negligible numbers lost to follow-up since people in Norway have a low tendency to emigrate, and the registries having been run for decades. Moreover, the linkage is of high quality due to the unique personal identification number. Unselected materials like nationwide materials, like ours, are necessary for incidence estimation.

Limiting factors with registry-based studies are the lack of detailed cancer treatment information, lack of prognostic factors, and lack of medical information on the offspring after the first days of life. Since treatment is notified only in broad terms, and restricted to the first four months after diagnosis, no treatment variables are used in this thesis, since we doubt that the whole treatment period is reflected, especially for patients who have received multimodal treatment. Instead, general national treatment routines are used (table 1, paper I) to stratify by treatment-related changes.

Hospital-based studies are useful supplements to register-based studies since they often provide more detail regarding treatment and prognostic factors, but have short-comings regarding selection, and cannot provide reliable incidence rates. Paper I and II, in comparison with similar studies conducted among patients from the Norwegian Radium

Hospital, reveal considerable differences between the studies regarding patient population, explaining, at least to some degree, the different results for some of the analyses.<sup>1;2;66;160</sup>

With registry-based materials, there is uncertainty or underreporting of certain variables, and other variables have been introduced more recently. Several examples are listed above; additionally, gestational length might be misclassified for some individuals since the date of last menstruation might be uncertain, and the reasons for caesarean section are underreported. Prognostic factors like serum tumour markers, hormone receptor status, tumour depth, and detailed stage or grading information are not routinely registered in cancer registers. Some of the above-mentioned factors are registered during the most recent years, but could in our study only be considered in specific subgroup analyses. This is a limitation of ours and similar studies, which can only be solved by adding information from the medical records for each patient, which would have been time-consuming and costly. There is no doubt that the reliability would have been increased further, if all of the accepted prognostic risk factors could have been adjusted for.

With reproduction as the main outcome, there are several limitations in our material. We do not have knowledge about partner status at diagnosis, or pre- and post-diagnostic wishes for children, nor do we know anything about failed attempts to get pregnant after cancer. Such information would have been available only if a survey was added to the registry-based material, or partly, with information from the individual's medical records.

## General discussion of the results

### **Are pregnancy rates after cancer lower than in the general population, and are there differences regarding cancer type and treatment?**

We found a reduction in pregnancy rates after cancer of 25% among male cancer survivors and 40% among female survivors compared to their controls. Separated by cancer types, only malignant melanoma and thyroid cancer survivors did not differ from their controls. Other authors reports similar findings.<sup>2;23;24</sup> A recent paper based on a Swedish cohort had similar findings; female cancer survivors were 27% less likely to give birth after cancer, compared to the cancer-free background population at a similar age.<sup>171</sup> Somatic changes related to the cancer are most probably the primary explanation for these observations, with treatment leading to sub- or infertility as the main reason. Gonadotoxic chemotherapy is probably the major explanation why survivors of leukaemia, partly HL, breast, and ovarian cancer have low associated pregnancy rates.

Reasons other than infertility might also influence the pregnancy rates after cancer.

Several smaller studies with questionnaires have been performed, which cover information of marital status at diagnosis and desire for future children. The wish to have a biological child is deeply rooted, and it has been shown that the majority of individuals still want children even after a serious illness like cancer.<sup>28;172</sup> However, survivors of testicular and cervical cancer are shown to face higher risks of splitting up with their partners after cancer.<sup>26</sup> Psychosocial and socioeconomic factors cannot be excluded with regard to parenthood after cancer, even though we could not adjust for them. A part of these psychosocial concerns, which might be limiting post-cancer parenthood, may be the fear of recurrence or fear of transferring cancer or anomalies to potential offspring. Furthermore, infertility or unmet desires for future children are associated with decreased quality of life and psychological distress, both among cancer survivors and the general population.<sup>173</sup>

### **Do male cancer survivors have higher fertility rates than female survivors?**

The results point to the gender difference, with a higher probability for male than female survivors to have children after cancer: HR=0.74 (95% CI 0.71-0.78) and HR=0.61 (95% CI 0.58-0.64), respectively. Regarding age at diagnosis, we found that also the youngest age-group, 16-25 years, had quite similar results (HR = 0.70 (95% CI 0.65-0.75) and HR = 0.67

(95% CI 0.63-0.73) for males and females, respectively). One would expect that a cancer diagnosis before the age of 25 in females would be protective with regards to the ovarian capacity, and the results are slightly better for women aged 25 years or less at diagnosis. There might also be other factors like type of cancer and treatment that influence the post-cancer pregnancy rates.

Regarding fertility-preserving efforts, males have been offered semen cryopreservation for decades, and the vast majority are able to do this because of impaired general condition at the time of diagnosis. Recovery is seen in sperm samples, but for some males, the time to recovery or to when satisfactory sperm cell account and motility is seen will differ.<sup>10,174</sup> In cases of post-treatment subfertility, ICSI can be performed, even if the sperm cell number is low.

For females, the situation is far more difficult, but experimental initiatives like ovarian tissue cryopreservation seem promising, especially for young females. The crucial point in many cases is to give proper counselling, since most methods for fertility-preservation require a period of hormonal stimulation for females, except for cryopreservation of ovarian tissue. Fertility should be discussed with newly diagnosed cancer patients on equal terms with other side effects that might occur as a result of the planned treatment. The literature shows that fertility issues are discussed more often with male than female cancer patients (males given information 14 times more frequent than females), both the risk of sub- or infertility, and possible fertility-preserving efforts.<sup>172</sup> Historically, counselling of female patients about subsequent pregnancies might have differed throughout the period studied, with more reservations earlier, especially for cancer types regarded as hormone-sensitive. The attitude towards initiating a pregnancy when having a history of cancer might also be different, both between genders, but also at an individual level.

Costs of infertility treatment are part of the tax-funded health care system in Norway and other Nordic countries, with three attempts usually covered for each couple, and a sum of about 2000 euro for one's own account. The majority of cancer survivors will retain or regain their fertility after treatment. The difficult part is the individual vulnerability for the treatment, and for females the biological time of decrease in fertility and menopause which is not known. The risk of POF cannot be detected pre-treatment today, even if AMH is

considered a promising parameter. A recent study revealed a pre-treatment measure of AMH as a predictive measure of post-treatment fertility, with higher precision than age at treatment.<sup>175;176</sup>

### **Have fertility-preserving efforts resulted in increased fertility-rates after cancer for selected cancer types?**

For ovarian cancer stage I, a significant improvement was seen during the study period (HR = 0.19 [95% CI 0.11-0.32] to HR = 0.67 [95% CI 0.49-0.90]). Testicular cancer underwent a significant change from the 1980s to the 1990s, where RPLND was performed bilaterally in the first period, and unilaterally in the second: HR = 0.51 (95% 0.45-0.59) to HR = 0.76 (95% CI 0.70-0.83), respectively. For males with HL, a tendency of higher rates of children after cancer was seen after ABVD was introduced. Further details in treatment changes are explained in the background chapter and in paper II.

For cervical cancer stage I, we did not see such an expected increase during the period; however, the fertility-preserving surgical methods have been applied since the 1970s, which practically cover the whole study period.

### **Are congenital anomaly rates in offspring born to cancer survivors equal to those in the general population?**

The vast majority of cancer survivors who had subsequent children gave birth to healthy infants. For all cancer types combined, no increased risk of congenital anomalies was found. The risk of adverse pregnancy outcome, especially foetal death and congenital anomalies, is a major concern for cancer survivors. In our population-based material, the number of outcomes is still small for many subgroups, calling for careful interpretation. There are some other population-based materials published from the other Nordic countries, with different results.<sup>2;177</sup> This might be due to differences in design. It emphasises the necessity of even larger materials to answer these questions. Several studies are performed on childhood cancer survivors, not showing any increased risks of congenital anomalies in the offspring.<sup>178-180</sup>

Ståhl *et al.* have recently published a study based on a population-based material including all males in Sweden and Denmark with a history of cancer and fathering a child afterwards,

finding that the risk of congenital anomalies in the offspring was increased after all cancer types seen together. They analysed all children born after cancer, regardless of parity. The sites for the cancer types associated with higher risks of anomalies were skin, eye, and central nervous system, which probably include a large proportion of survivors from malignant melanoma. The offspring of survivors of testicular cancer or haematological malignancies did not differ from the cancer-free populations' offspring.<sup>177</sup> Compared with the findings of the study by Magelssen *et al.*, regarding altered risk of anomalies among the offspring, based on a hospital-based material from the Norwegian Radium Hospital, the cancer types differ. Magelssen's study reports testicular cancer and malignant lymphoma as the most frequent cancer types for males who fathered a child with an anomaly.<sup>2</sup> The difference between the findings from these two studies including male cancer patients could probably be caused by chance findings, since congenital anomalies are rare events. At least, there is little evidence for concluding that specific cancer types impose higher risks of anomalies among subsequently born offspring.

As described in the results, there were considerably larger differences between the materials used for the studies by ourselves and Magelssen, with regard to the number of malignant melanoma patients. The hospital-based study found that male survivors had an increased risk of a baby with a congenital anomaly, while we did not find that; this could reflect the selection of patients referred to the Norwegian Radium Hospital, with a higher number of more severe cases needing more treatment.

### **Are adverse pregnancy outcomes like perinatal death, preterm birth and low birth weight more frequently seen in infants delivered by female cancer survivors than in offspring of females without cancer?**

Increased risks of preterm birth and LBW at term were found among offspring of female survivors compared to their controls, and more often among primiparous than nulliparous survivors. However, other authors have reported contradictory results regarding perinatal death, preterm birth, and LBW after female cancer.<sup>2;23;74-78</sup> Higher frequency of perinatal death among cancer survivors was demonstrated recently to be associated with the time since cancer, which is comparable with our findings with higher risks if the pregnancy was initiated during the first two years after the diagnosis of malignancy.<sup>181</sup>



Our findings of different risk patterns with higher risk estimates of preterm birth, LBW and even perinatal death for primiparous than for nulliparous female survivors have not been previously reported, to the best of my knowledge. It is unclear what the mechanisms are. The arguments of having a pregnancy after cancer might be different for those two groups. Since primiparous female survivors have already experienced pregnancy, it might be easier to undergo a second one, even after a serious disease like cancer. Also, the threshold may be equivalently higher for nulliparous individuals, so only the healthiest ones will choose to get pregnant. There might also be age-dependent effects that influence the primiparous group more than the nulliparous group. This could probably involve a similar mechanism as seen for the development of POF effects mediated from the cancer treatment increasing the biological age, at least in some organs.

We found a higher incidence of pre-eclampsia among primiparous cancer survivors than among primiparous females without cancer. This might be due to the toxic effects of the cancer treatment, especially chemotherapy, inducing oxidative stress. A similar finding has been reported recently in a case report with a pregnant woman treated with chemotherapy already from the first trimester for breast cancer. She was gravida 4, para 1, and developed severe pre-eclampsia, leading to acute caesarean section in gestational week 36.<sup>182</sup> There has been no other report of such findings, to the best of my knowledge.

The usual increase in birth weight from sibling one to sibling two is about 140 grams.<sup>183</sup> Magelssen *et al.* found a decrease in birth weight for the second sibling when the mother had cancer before the second pregnancy, and we found a similar difference for the subpopulation of female cancer survivors without malignant melanoma, with only a slight weight increase from the first to second baby (37 grams compared to 146 grams increase from first to second baby among the controls).<sup>184</sup>

### **What is the incidence of pregnancy-associated cancer?**

The incidence of cancer during pregnancy is most often described as 1:1000.<sup>80;81</sup> We found an incidence of about 1:4000 for the whole study period if only the pregnancy period was included, and 1:2000 if the first six months postpartum were included. This might reflect differences in different populations, and different definitions of “during pregnancy” as some authors include the first postpartum year as well, especially for breast cancer. It also reflects

that such numbers are based on few large materials, and reflect a relatively rare situation, therefore requiring the tag “estimated incidence”, due to random variation.

Incidence should be based on population-based materials, and might be wrongly determined if materials are hospital-based or selected in other ways. Examples are the frequently published statement that breast cancer (or eventual cervical cancer) is the most common cancer type diagnosed during pregnancy, and the conflicting results regarding pregnancy outcome in offspring of cancer survivors. Breast cancer is the most common cancer type in the age group 16-45 years, but not the most frequent diagnosis during pregnancy, lactation or in the group of females with a subsequent pregnancy, since other cancer types like cervical cancer, brain tumours, and lymphoid and haematopoietic malignancies are more common until the mid-thirties.<sup>3</sup> We found that malignant melanoma is by far the most frequent cancer type both during pregnancy and lactation, with cervical cancer being the second most common, and breast cancer third. Similar incidence rates have been reported by others.<sup>98</sup>

Incidence is a matter of external validity, since generalisation of the results also depends on ethnicity and different risk patterns for developing cancer. With the knowledge of high incidence of cutaneous malignant melanoma in Norway and fair-skinned people living in Northern-Europe, the USA, Canada, Australia and New Zealand, the distribution of cancer types might differ among various skin types. Further, the median age at diagnosis is higher for breast cancer than for malignant melanoma. Breast cancer has a later onset than malignant melanoma (median age at diagnosis was 29 and 34 years old, respectively). This influences the numbers of females diagnosed during pregnancy, and even those who have a subsequent pregnancy. Since many of the papers only focus on one cancer type during pregnancy, and few studies are population-based, statements such as “breast cancer is the most common cancer during pregnancy” have come into being.

### **Is survival for females diagnosed with cancer during pregnancy poorer than for non-pregnant females, especially for selected cancer types?**

Breast cancer diagnosed during pregnancy has been postulated to implicate poorer prognosis, historically based on a hormone hypothesis, meaning that tumour cells are promoted by higher levels of oestrogen during pregnancy. Another crucial point is the

treatment; postponement of initiation and reduction of aggressiveness have probably been more common than the opposite. A third reason why cancer diagnosed during or shortly after pregnancy seems to be associated with adverse outcome, is the transient increased risk of breast cancer risk after a pregnancy, as this period is probably longer with higher maternal age.<sup>93;101;102;185</sup> A fourth (or maybe part of the third) explanation for the poorer prognosis of PABC, is the hypothesis about involution, a tumour promoting tissue microenvironment following pregnancy and lactation. After the cessation of breastfeeding, there is an involution of the breast, meaning a regression of the mammary gland in an inflammatory-like process, with increased immune cell influx and breakdown of the stroma surrounding the glands and the ducts. The changes occurring are postulated to enhance tumour growth and the growth of metastases.<sup>93;94</sup> A Norwegian study reported a high proportion of poorly differentiated tumours, partly explained by young age, in women with a recent childbirth.<sup>186</sup>

The hormonal hypothesis, for breast cancer in particular, is presumably not the main reason for the adverse prognosis for those diagnosed during pregnancy. Since several studies reveal similar prognosis compared to the non-pregnant population, while stage is properly adjusted for, it is time to question this hypothesis. Similarly, for malignant melanoma, reassuring results were found in our study and two other large studies.<sup>115;116</sup>

Most malignancies seem to be diagnosed at a later stage when they occur during pregnancy and even post-partum. The young age of the patients and the gestational symptoms might mislead physicians to interpret the symptoms as caused by the pregnancy or lactation, instead of by a malignancy. Several studies regarding gestational malignant melanoma and breast cancer reveal the more advanced stage at diagnosis among the pregnant patients compared to the non-pregnant.<sup>92;93;96;109;110;187</sup> This emphasises the advice to always biopsy a suspect mole, or consider diagnostic procedures as ultrasound and cytology of a suspect tumour in the breast of a pregnant or lactating woman. Mammography can be safely done post-partum, but interpretation might be more difficult for all imaging diagnostic procedures for women who are pregnant or lactating at examination.

In a recent paper by Johansson *et al.*, a Swedish material was investigated, and they stated increased mortality in women with breast cancer diagnosed during or shortly after

pregnancy. A crucial limitation of that study was the lack of adjustment for extent of disease.<sup>188</sup> In our analyses, extent of disease was the most important factor for the covariates, as shown in *Table 4*. The same group have more recently published a paper where stage at diagnosis is adjusted for, but with a smaller number of patients. They then reported a mortality of HR = 1.27 (95% CI 0.88-1.83) when adjusting for stage, age, and calendar year.<sup>189</sup>

*Table 4*

*Breast cancer diagnosed during pregnancy or lactation period and survival\**

|   | <b>Dx during pregnancy<br/>HR (95% CI)</b> | <b>Dx during lactation<br/>HR (95% CI)</b> |
|---|--|--|
| <b>Unadjusted</b>                           | 1.76 (1.20-2.56)                           | 3.46 (2.43-4.93)                           |
| <b>Adjusted for age at diagnosis</b>        | 1.41 (0.95-2.08)                           | 2.67 (1.87-3.81)                           |
| <b>Adjusted for calendar period</b>         | 1.83 (1.24-2.69)                           | 3.47 (2.44-4.94)                           |
| <b>Adjusted for extent of disease</b>       | 1.29 (0.88-1.90)                           | 2.40 (1.68-3.42)                           |
| <b>Adjusted for age, period, and extent</b> | 1.23 (0.83-1.81)                           | 1.95 (1.36-2.78)                           |

*\*The table contents the hazard rates for cause-specific survival of breast cancer, if diagnosed during pregnancy or lactation, compared to those who not where pregnant or diagnosed during the first 6 months post-partum. Estimates for each one of the covariates are given, and at last, the completely adjusted HRs. The table is extracted from the background statistics for the paper "Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study"(paper III).<sup>164</sup>*

However, Johansson *et al.* have an interesting story told by the numbers themselves: They found 107 patients diagnosed with breast cancer during pregnancy (defined as a 9 month long period prior to birth), 140 diagnosed during the first 6 months post-partum, 281 during 7-12 months after birth, 296 during 13-18 months post-partum, and finally 286 women diagnosed during 19-24 months after birth.<sup>188</sup> The high increase in incidence from the last part of the first year post-partum compared to the lower numbers during pregnancy and the first 6 months post-partum might be explained by a delay in diagnosis. This finding might also be regarded an effect of transient increased risk of breast cancer after a pregnancy (this might be potentiated by the selection of pregnancies; if there were more than one pregnancy during the observation period, the second one was chosen), and finally maybe by the involution hypothesis.

Our approach to dividing pregnant and lactating cancer patients takes into account the treatment differences that might influence an aggregated group (gestational cancer). Cancer

diagnosed during pregnancy might be differently handled than tumours diagnosed during lactation, taking the foetus into account. Authors have argued that subgroups, like those presented here, are of no use, since the cancer most likely started to grow long before the pregnancy was initiated.<sup>94</sup> For some of the cancer types, especially breast cancer, which we know has a dualistic risk pattern after pregnancy, it can be useful to include longer time intervals. For all cancer types seen together, I believe it still can be useful to analyse pregnant and lactating patients separately, to take eventual differences in diagnostics and treatment into account, even if most malignancies originated before the pregnancy or lactation period started.

History has revealed how counselling can seriously influence a patient's life. Examples are consideration of the necessity of castration of pre-menopausal women diagnosed with breast cancer, which not only eliminates the possibility of becoming pregnant, but also introduces other possible adverse side effects. Further, advice about the termination of concurrent or subsequent pregnancies for women diagnosed with breast cancer and even other cancer types like malignant melanoma has been given, which we today know is unnecessary. Historical data, at least for breast cancer and malignant melanoma, evidenced mainly by case-reports published from the 1950s and onwards, did not leave much hope for the prognosis of those diagnosed during pregnancy.<sup>84;103</sup> It is easy to understand that pregnant patients with poor outcomes made deep impressions on the clinicians, but with today's knowledge, several decisions were taken based on weak evidence. We will never know how much a delay in treatment or lack of treatment influenced this group, compared to the non-pregnant proportion of the cancer patients of similar age.<sup>86-88;103</sup>

Today, thanks to reports from dedicated physicians and the collection of data, we know more about cancer treatment during pregnancy, and what harms the foetus and what most likely does not.<sup>72</sup> Guidelines regarding diagnostics and treatment are to be published, like, for instance, the French recommendations for cervical and ovarian cancer diagnosed during pregnancy and recommendations based on consensus meetings.<sup>8;85;190-192</sup> Proper counselling and decision-making needs to be evidence-based as far as possible. Still, it seems that the new knowledge has not yet been fully incorporated, and that clinicians do not dare give cancer treatment during pregnancy: A recent survey revealed that current treatment is not in line with recent evidence, with several more terminations and delays of maternal treatment

than necessary. University clinics had the best outcome in this European survey, compared to non-academic hospitals.<sup>193</sup>

Another fear of cancer during pregnancy is the risk of the transmission of malignant cells to the placenta and to the foetus. As described earlier, it is extremely rare that placental invasion is detected, and even rarer that the foetus is involved. For all females who are diagnosed with cancer during pregnancy, the placenta should be properly examined, with macroscopic and histopathological methods, including cytology of maternal and umbilical cord blood. The infants should obviously be thoroughly examined as newborns, with regular follow-ups during of the first years of life. In a recent review, a total of 87 cases have been described during the 20<sup>th</sup> century, with 19 cases involving the foetus. Malignant melanoma (31%) and breast cancer (17%) are the two most common cancer types with placenta and/or foetal metastases,<sup>194</sup> followed by NHL and leukemia.<sup>82;137</sup>

### **Do female survivors with subsequent pregnancies have poorer survival than those not becoming pregnant after cancer?**

We did not find that women with pregnancies after cancer had any inferior survival in our study.<sup>164</sup> Few contemporary studies report adverse survival for females becoming pregnant after cancer. The exception is those becoming pregnant very shortly after cancer.<sup>67</sup>

Also, a recent study based on Swedish and Singaporean material has shown lower mortality rates for breast cancer survivors with subsequent pregnancies than for breast cancer survivors without pregnancies after cancer; however, in comparison with women in from the background population at similar age, cancer survivors with subsequent pregnancies had higher mortality rates.<sup>195</sup>

## SUMMARY AND CONCLUSIONS

### **Paper I**

Cancer survivors of both genders have significantly lower pregnancy rates after diagnosis than controls in the same age group. For all cancer types seen together, the pregnancy rates for males were reduced by 26% and for females by 39%. However, a diagnosis of malignant melanoma or thyroid cancer did not affect the pregnancy rates. Fertility-preserving anti-cancer treatment has showed a positive effect for females with ovarian cancer and males with testicular cancer and HL, since their pregnancy rates increased during the study period.

### **Paper II**

We did not find any increased risk of adverse birth outcome for the male survivors' offspring; in particular, no increased risk of congenital anomalies was seen. Risk of preterm birth after cancer was increased by 90% among primiparous and by 30% among nulliparous female cancer survivors. For the offspring of primiparous female survivors, an increased risk of LBW and perinatal death emerged. Higher parity might be associated with higher risks of adverse birth outcomes after cancer.

### **Paper III**

The incidence of pregnancy-associated cancer was 1:2000. Malignant melanoma, cervical cancer and breast cancer were the most frequent cancer types during pregnancy or lactation, in that order. Cancer diagnosed during pregnancy was not associated with an increased risk of cause-specific death for all cancer types combined. Malignant melanoma diagnosed during pregnancy represented an exception, with a borderline increased risk. Cancer diagnosed during the lactation period did not increase cause-specific death, except for females diagnosed with breast or ovarian cancer. Patients with malignant melanoma or those with breast or ovarian cancer could all be at risk of delayed diagnosis, as the symptoms could be interpreted as pregnancy or post-natal conditions. None of the cancer types were linked to worse survival for those who had subsequent pregnancies.





## FUTURE PERSPECTIVES

For all of the topics assessed in this thesis, nationwide materials like ours are still small when the numbers of events are rare or the subgroups are small, even though the study period ranged over several decades. An expanded cohort, for example a Nordic material based on information from cancer registries and birth registries, would decrease the possibility of chance findings and increase the reliability. In such an expanded material, childhood cancer might also be included, enabling the assessment of differences among age-groups and different cancer types, regarding fertility after cancer and birth outcomes for the offspring. To further strengthen the results, information from medical records like prognostic factors and detailed treatment information would be desirable, either through requests for such information to the hospitals, or more efficiently, through already established quality registers. There are several areas where further research is needed:

### **Fertility and cancer:**

- Provision of personalised cancer treatment when possible based on fertility potential and wishes at the time of cancer diagnosis, taking the chance of cancer cure into account. Proper information about fertility potential and methods to preserve it should be given at diagnosis.
- Guidelines should be created for relevant subgroups with information about reproductive health after cancer treatment, including estimations of the possibility of post-cancer parenthood and/or possible techniques to preserve fertility. In particular, there is a need for putting experimental techniques for fertility-preserving methods for women into effect.
- The role of AMH needs to be further explored; is a pre-treatment level predictive enough, together with age, to counsel women about the need for fertility-preserving efforts like ovarian tissue cryopreservation or not? Is AMH reliable enough post-treatment to predict ovarian functioning and estimate menopausal age?

### **Birth outcomes of cancer survivors:**

- Further research is required into the effects of parity, since our study revealed higher risks of adverse birth outcome for primiparous compared to nulliparous females who became pregnant after cancer treatment.

- Assessing birth outcome after cancer (congenital anomalies and perinatal death) in an expanded cohort, for example using a Nordic material, because of contradictory findings.
- Perform long-lasting follow-up studies of offspring who have been exposed to cancer treatment *in utero*, maybe based on international registration.

### **Cancer during pregnancy:**

- Develop guidelines for multidisciplinary cancer care of women confronted by a malignant diagnosis during pregnancy in order to offer optimal diagnostics and treatment with a maximal chance of cure of the mother and minimal risk for the infant *in utero*. Establish a (national) referral system in order to centralise specific expertise, for the best care of the mother and child.
- Develop guidelines for the follow-up of women pregnant subsequent to a cancer diagnosis.
- Further studies on the survival of females diagnosed with cancer associated with pregnancy need to explore prognostic factors, e.g. to determine whether HER-2 negative and positive breast cancer tumours during pregnancy have different outcomes, if malignant melanoma site, tumour thickness, or certain skin types have poorer prognosis than others, and if there is a difference in prognosis if the malignancy is diagnosed during pregnancy or shortly thereafter.

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## Errata

In paper III, table 2, the correct number of lymphoma and leukemia patients pregnant after cancer that died in the group OAS 60; i.e. overall survival at age 60, should be 33, and not 272, as listed.



## Publications I-III















